Development and Background of the Magnesium Stent

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disclosures

- Consultant Biotronik
- Consultant Medtronic

Introduction to BioResorbable Scaffolds (BRS)

Rationale

For vascular therapies, late stent thrombosis and restenosis,

due to permanent drug-eluting stents, are persistent problems. [1,2]

An ideal vascular scaffold[2]

↓

Would **support the vessel with adequate radial force** to prevent elastic recoil during healing

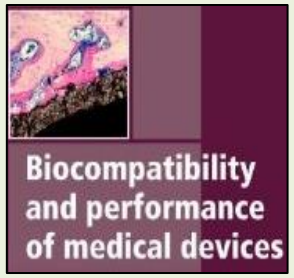
↓

and **disappear at the same rate as the vessel heals**,

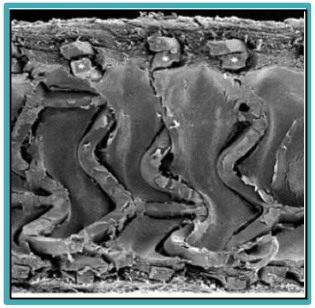
restoring normal vessel reactivity

1. Bonan R, Asgar AW (2009) Interventional Cardiology Biodegradable Stents- Where Are We in 2009?. Interventional Cardiology 81-84.
2. Waksman R (2006) Update on bioabsorbable stents: from bench to clinical. J Interv Cardiol 19: 414-421.

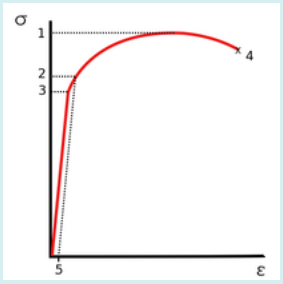
Which material selection criteria are important for a BRS?



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, higher strength for higher radial force)

1. Heiden et al., J Biotechnol Biomater 2015
2. Garg et al. Biodegradable and non-biodegr. Stents, Minerva Cardioangiol 2009;
3. Wikipedia: https://en.wikipedia.org/wiki/Tensile_strength Date 28.08.2015

Natural elements: biocompatibility, resorption profile & mechanical properties

Natural elements

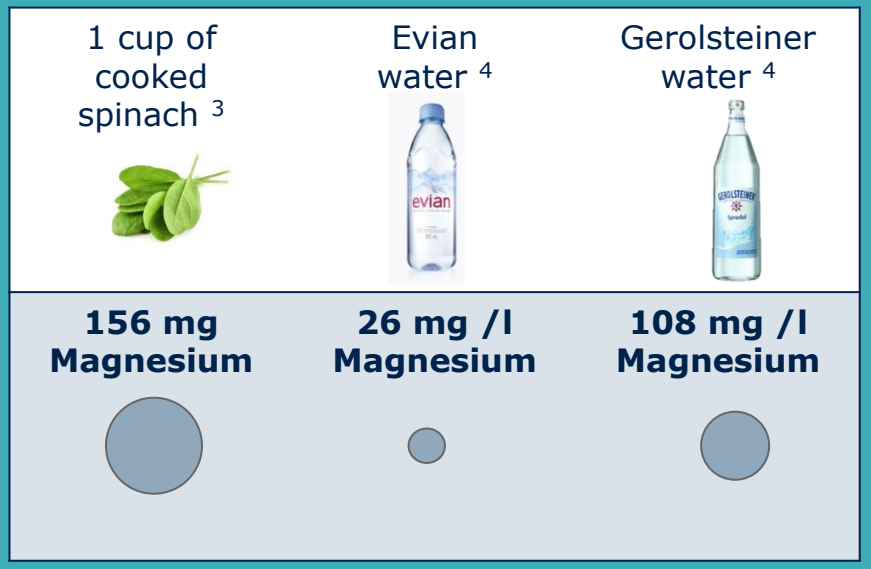
- Alloys of two elements have been investigated: Magnesium and Iron
- Elements with high natural occurrence in the human body are most appropriate for scaffolds because this ensures maximum biocompatibility
- Depending on the alloying elements and processing of the alloy, various resorption times and mechanical properties can be obtained.
- Scaffolds of natural elements have the potential to offer mechanical properties comparable to a permanent stent.

Why is Magnesium the preferred element for the development of a BRS?

Magnesium (Mg) is a common natural element in the human body[1]

- Magnesium is the fourth most abundant mineral element in the body[2]
- It is essential for the activity of over 300 enzymes [1]
- The total body content is ~ 20g [1]
- The daily intake need is ~ 350 mg

Magnesium intake



1. Garg et al. Biodegradable and non-biodegr. stents, Minerva Cardioangiol 2009;
2. Arnaud M. Update on the assessment of magnesium status. *The British Journal Of Nutrition*. June 2008;99 Suppl 3:S24-S36
3. Institute of Medicine (US) Evaluation of Dietary Reference Intakes.. Washington, DC: National Academies Press, 1997
4. Gerolsteiner.de

Summary of the material properties for metallic alloys, Magnesium and common polymers

Material (Alloy)	Biocompatibility	Resorption [months]	Tensile strength [Mpa]	Elongation at break [%]
Stainless Steel (316L)	+	n.a.	670	48
Cobalt Chromium (L-605)	+	n.a.	> 1.000	> 50
Pure Iron	+/-	> 12	210	40
BIOTRONIK Magnesium Scaffold	+	≈12*	280	6.8
Poly-L-lactide Acid	+	18 - 36	40 - 65	2 - 6**

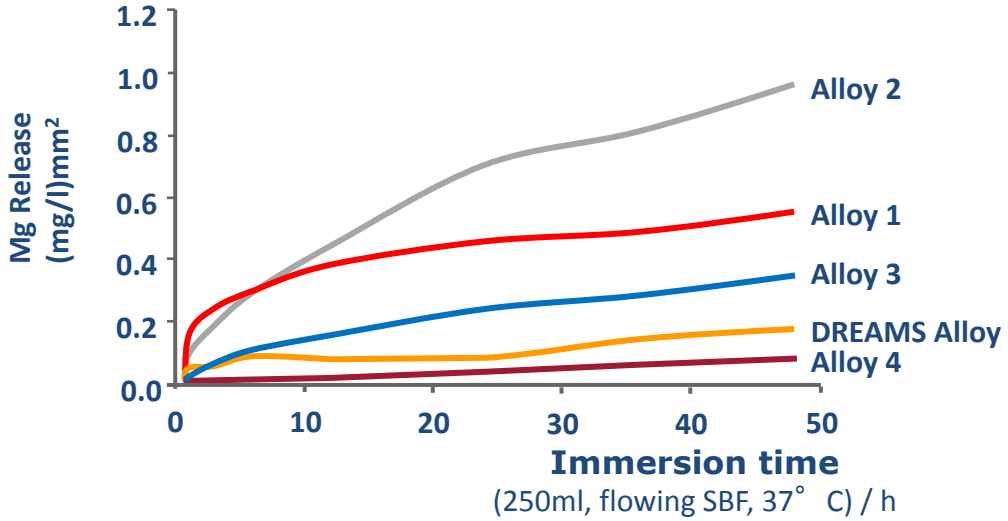
*Data on file

** Indicative value for raw material

Tailor-made Magnesium alloy provides the best balance to fulfill the key requirements of a BRS

Source: Foin et al, Impact of stent strut design in metallic stents and biodegradable scaffolds, Int J Cardiol 2014

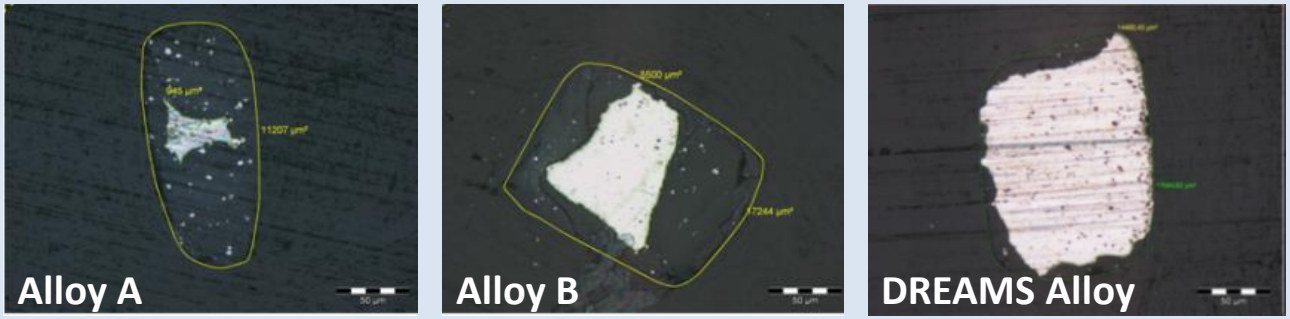
Not all magnesium alloys are the same



(250ml, flowing SBF, 37° C) / h

- **Adding alloying elements to magnesium can significantly alter the absorption speed**
- **BIOTRONIK uses a tailor-made alloy**

Impact of purity and processing on absorption speed



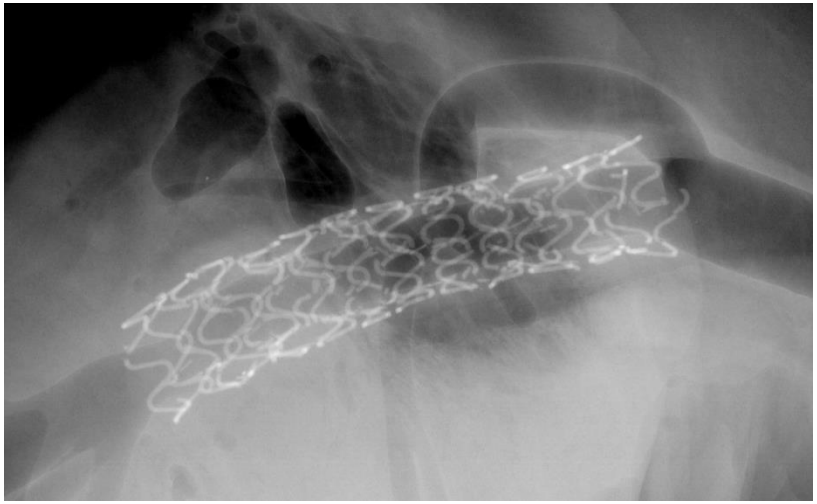
28-Day porcine coronary model

Line represents shape of original strut, white represents residual Mg core

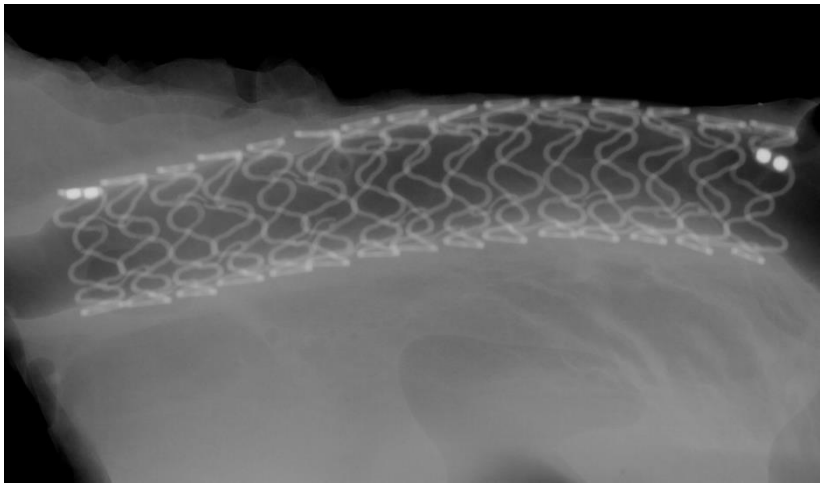
Prolonged scaffolding
Faxitron imaging 90 days

DREAMS
1st Generation

DREAMS
2nd Generation



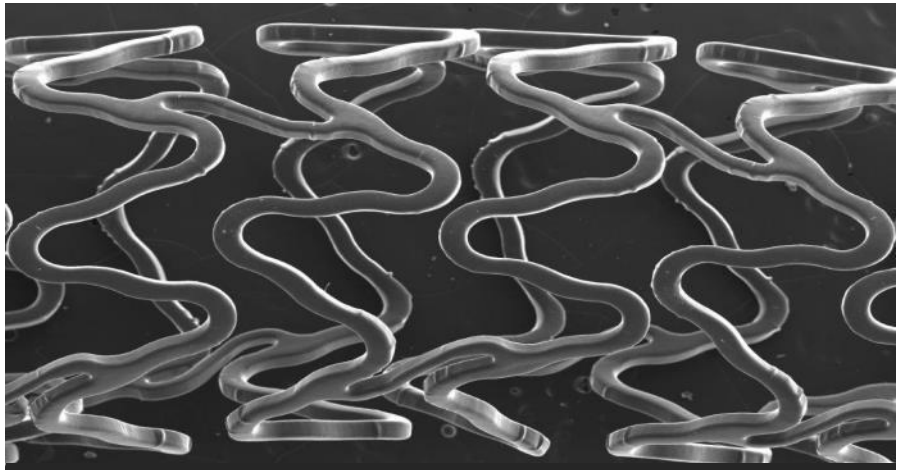
90d



Surface images of BIOTRONIK Magnesium Scaffold

Outer contour of bent stent 3.0 x 20mm (R=7.5mm)

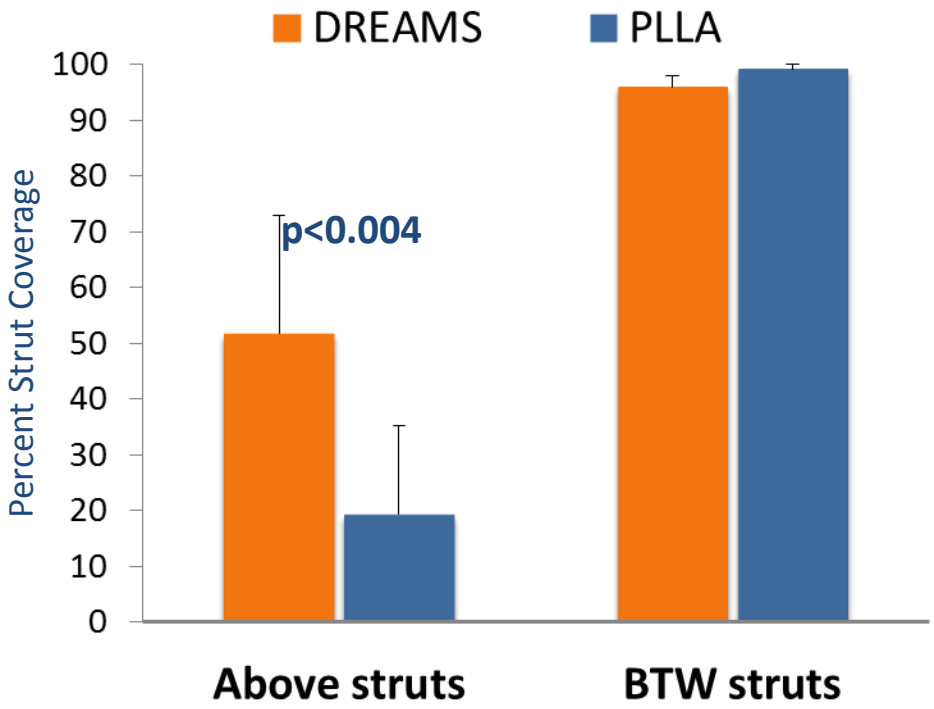
Rounded strut geometry may lead to smoother, better deliverability

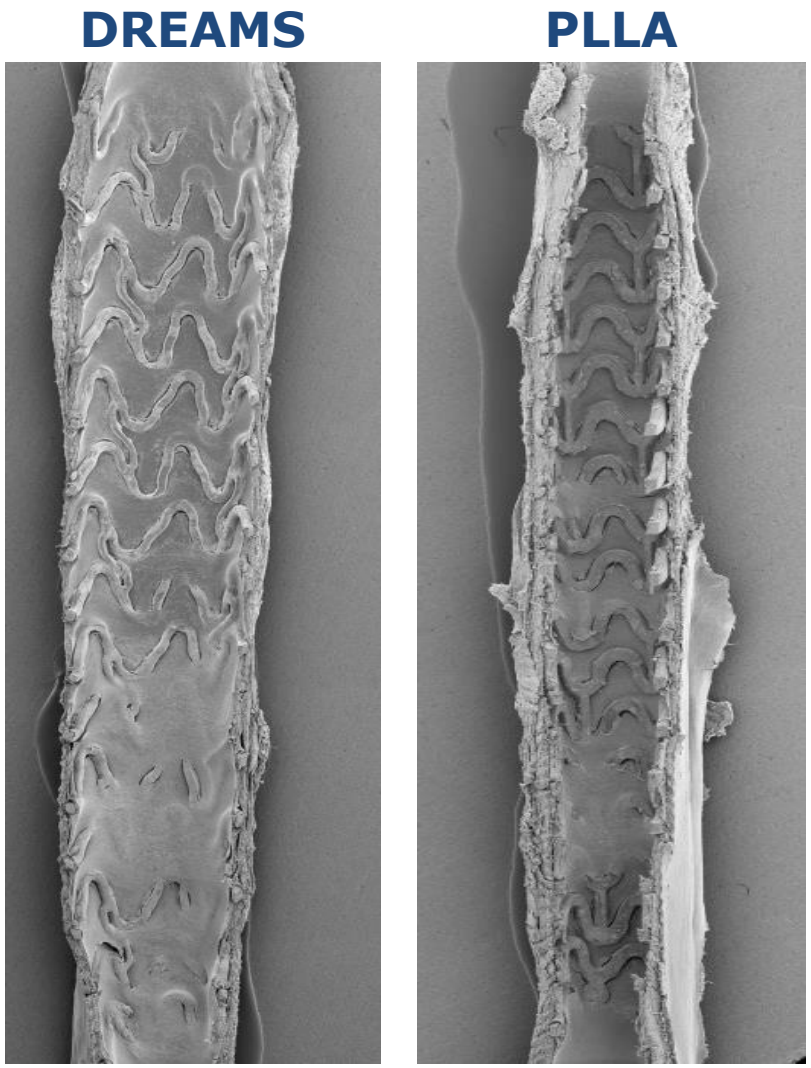


SEM images show smooth, stent-like apprearance

Endothelialization testing

in New Zealand white rabbits at 28-days

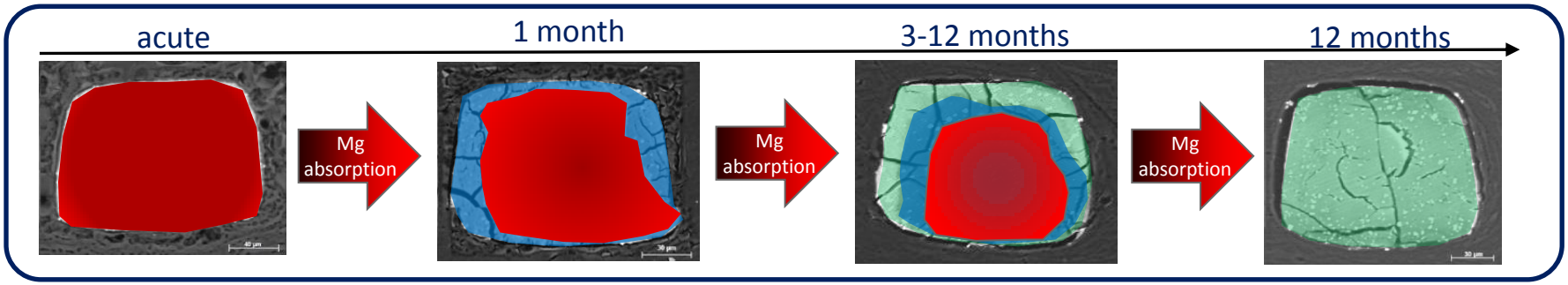




Source: Adapted from M. Joner, oral presentation, CRT 2015.

BIOTRONIK Magnesium Scaffold

Magnesium Absorption Process



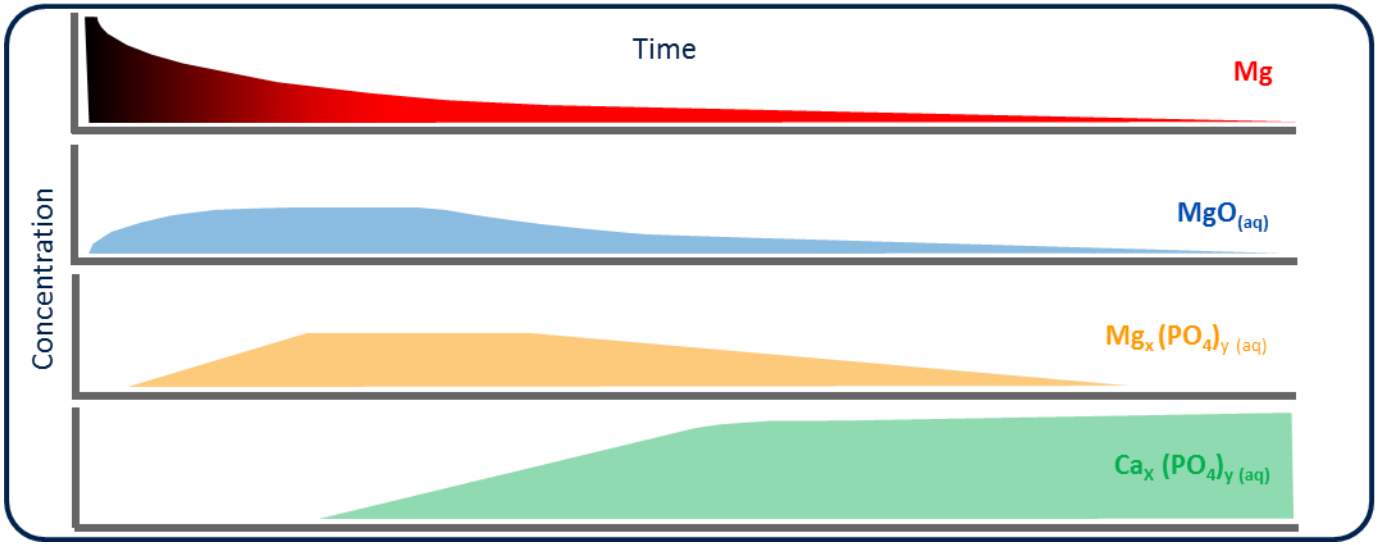
$$Mg + H_2O \rightarrow MgO_{(aq)} + H_2$$

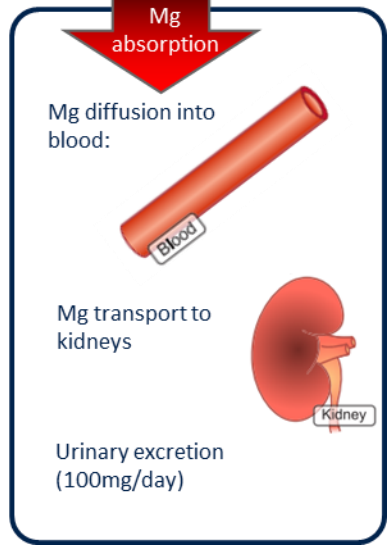
$$MgO_{(aq)} + PO^{3-}_{4(aq)} \rightarrow Mg_x(PO_4)_{y\ (aq)}$$

$$Mg_x(PO_4)_{y\ (aq)} + CaO_{(aq)} \rightarrow$$

amorphous calcium phosphate

$Ca_x(PO_4)_{y\ (aq)}$ + $Mg^{2+}_{(aq)}$





Magnesium Scaffold for achieving the optimal design requirements

AMS
2004

Mg
Alloy

No coating

No drug

Clinical study:

PROGRESS-AMS

Improvements:
- Mg alloy
- Backbone
- Coating
- Drug

DREAMS 1G
2010

Mg
Refined alloy

PLGA Polymer

Paclitaxel

Clinical study:

BIOSOLVE-I

Improvements:
- Mg processing
- Backbone
- Coating
- Drug

DREAMS 2G
2013

Mg
Refined alloy

PLLA Polymer

Sirolimus

Clinical study:

BIOSOLVE-II

BIOTRONIK Magnesium Scaffold (DREAMS 2G)

- A combination of proven Orsiro elements and the benefits of an resorbable Magnesium Scaffold

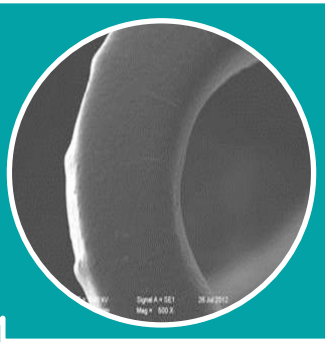
Backbone

Mg alloy

Tantalum markers

6-crown & 2-link design

150µm strut thickness



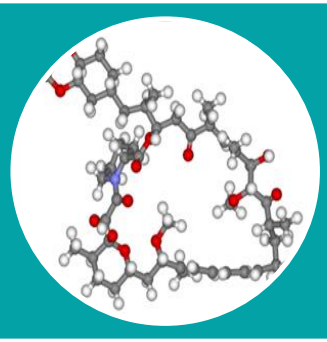
BIOlute

Coating

PLLA

Proven resorption profile

Proven technology identical to Orsiro coating



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

Safety and Clinical Performance of the Drug Eluting Absorbable Metal Scaffold in the Treatment of Subjects with de Novo Lesions in Native Coronary Arteries-BIOSOLVE-II

Michael Haude, MD

On behalf of the BIOSOLVE-II Investigators

Background

Evolution of the BIOTRONIK Magnesium Scaffold

		PROGRESS-AMS 	BIOSOLVE-I 	BIOSOLVE-II 
	Device generation	AMS	DREAMS 1G	DREAMS 2G
Design	Sizes (mm)	Ø 3.0 & 3.5 Length: 15, 20	Ø3.25 & 3.5 Length: 15	Ø 2.5, 3.0 & 3.5 Length: 15, 20, 25
	Backbone	Mg alloy	Refined Mg alloy	Refined Mg alloy
	Strut thickness/width	165/80 µm	120/130 µm	120/120 µm (Ø 2.5) 150/150 µm (Ø 3.0 & 3.5)
	Markers	none	none	Ta-composite
	Coating - drug	none	PLGA/PTX	PLLA/SIR
	Crossing profile in mm	1.6	1.5	1.75
Kinetics	Drug elution kinetics	n.a.	like Taxus	like Orsiro
	Absorption period in month	1-2	3-4 (Mg)	≈12 (Mg)
Results	In-segment Late Lumen Loss (mm)	0.83±0.51	0.52±0.48	?
	In-scaffold Late Lumen Loss (mm)	1.08±0.49	0.65±0.50	?
	TLF* (%)	23.8	4.3	?
	Definite or Probable Scaffold Thrombosis (%)	0.0	0.0	?

*Composite of cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization and CABG

BIOSOLVE-II

Study Design

DESIGN

- Prospective, multi-center, FIM. Single de novo coronary artery lesions in up to two coronary arteries, RVD between 2.2-3.7 mm and lesion length ≤ 21 mm

PRIMARY ENDPOINT

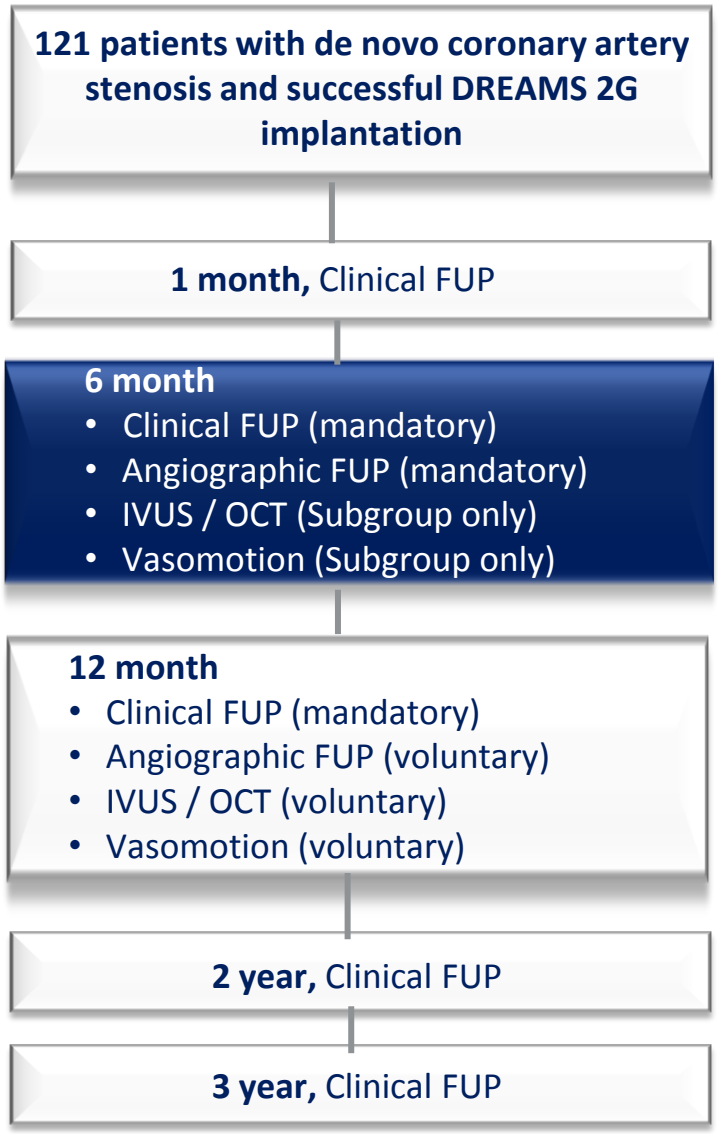
- In-segment late lumen loss @ 6-month

COORDINATING CLINICAL INVESTIGATOR

- Prof. M.Haude, Lukaskrankenhaus GmbH, Neuss, Germany

CORELAB

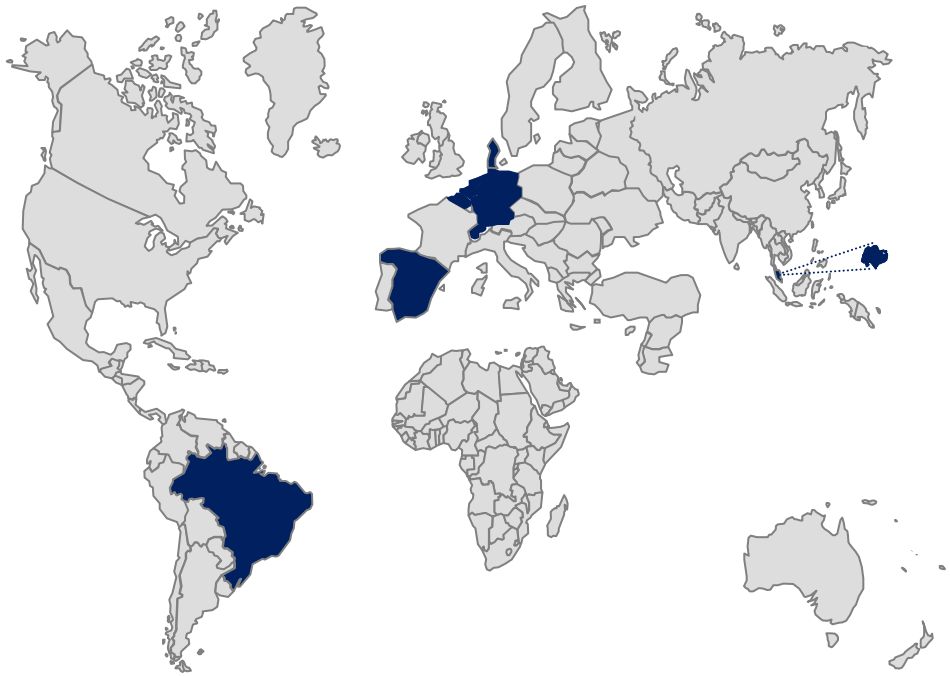
- Cardialysis, Rotterdam, The Netherlands



BIOSOLVE-II

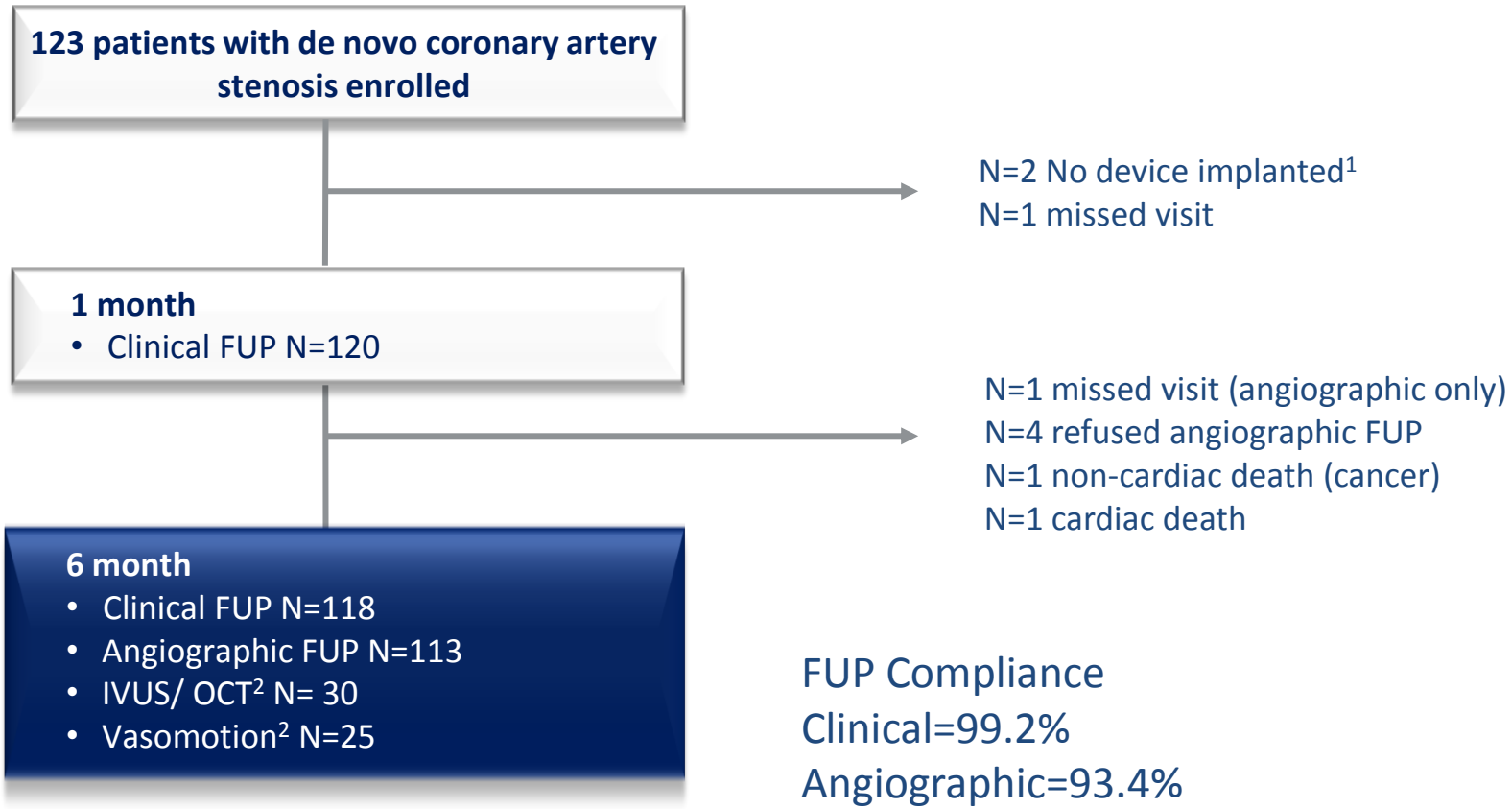
Investigational Sites

Investigator	Country	N
M. Haude, MD (CCI)	Germany	35
H. Ince, MD	Germany	17
A. Abizaid, MD	Brasil	13
R.Tölg, MD	Germany	13
P. Lemos, MD	Brasil	12
C. von Birgelen, MD	The Netherlands	7
E. Christiansen, MD	Denmark	7
W. Wijns, MD	Belgium	5
F.J. Neumann, MD	Germany	5
C. Kaiser, MD	Switzerland	3
E. Eeckhout, MD	Switzerland	2
S.T. Lim, MD	Singapore	2
J. Escaned, MD	Spain	1



BIOSOLVE-II

Patient Flow

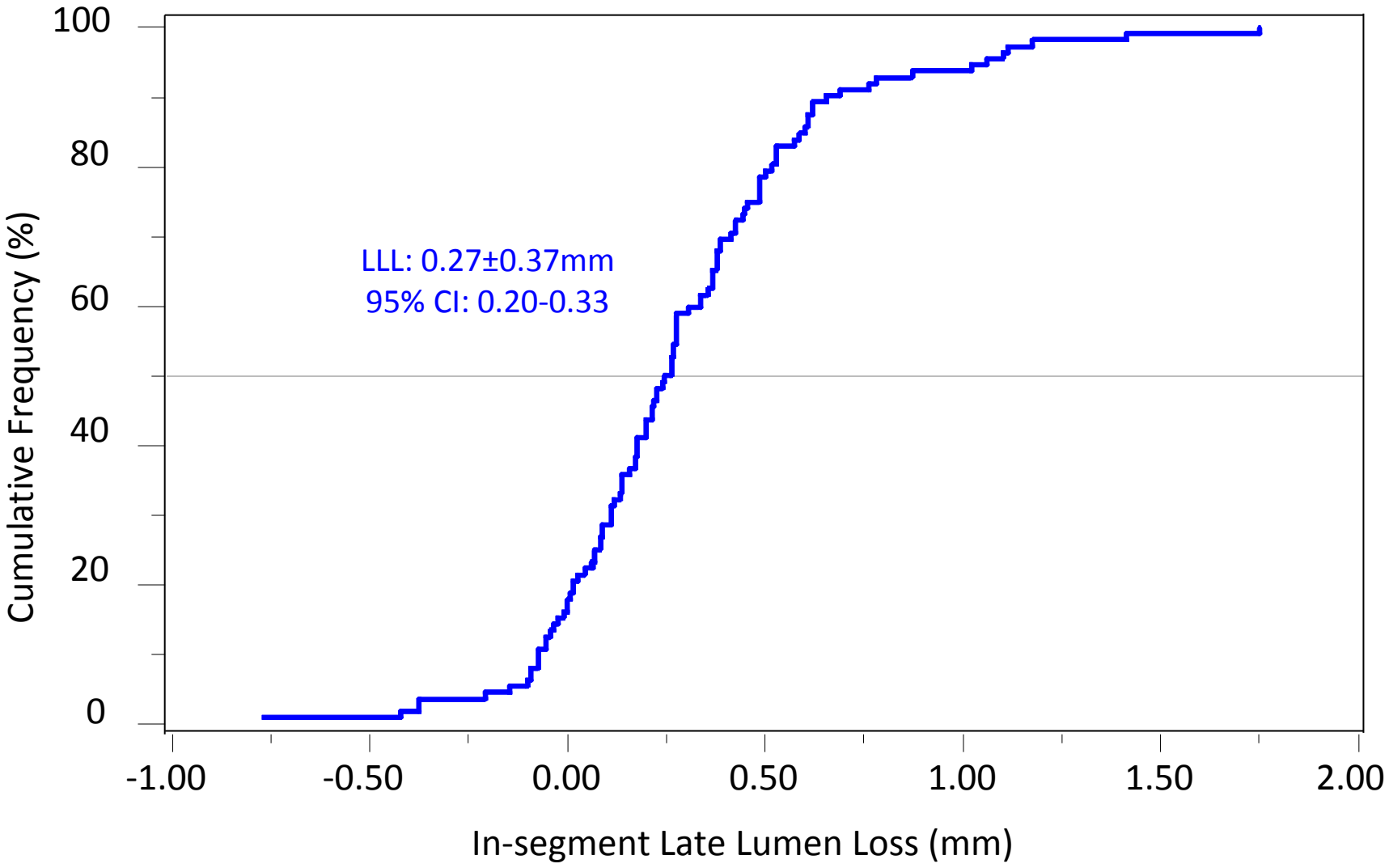


1. 2 subject who did not receive a DREAMS 2G were only considered for procedure and device success calculation as defined in the protocol
2. Subgroup only

BIOSOLVE-II

Primary Endpoint

In-segment Late Lumen Loss at 6-month



BIOSOLVE-II

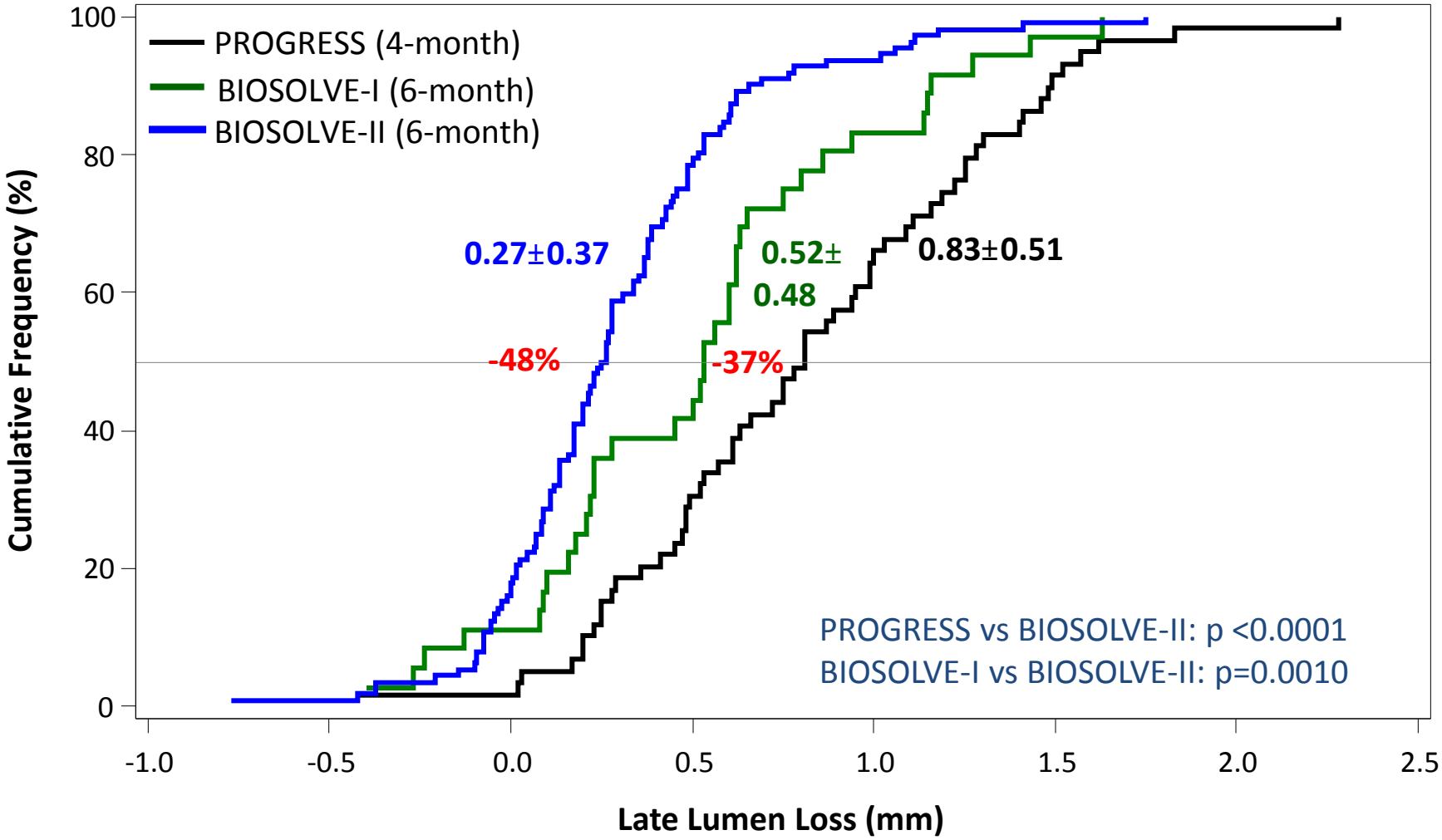
Clinical Results

TLF rate at 6-month

	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

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



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

BIOSOLVE-II

Conclusion

- DREAMS 2G in BIOSOLVE-II demonstrates significantly improved in-segment LLL (0.27±0.37mm) compared to its precursor devices tested in the PROGRESS (0.83±0.37mm) and the BIOSOLVE-I study (0.52±0.48mm)
- Vasomotion of the scaffolded vessel segment was demonstrated at 6 months
- IVUS results on a subgroup of 30 subjects demonstrate a preservation of the scaffold area with a low neo-intimal area at 6-month
- No intra-luminal masses were observed by OCT at any time on a subgroup of 30 subjects
- DREAMS 2G in BIOSOLVE-II demonstrates a low TLF (3.3%) and TLR (1.7%) rate at 6-month, which is comparable to other absorbable scaffolds and permanent drug eluting stents
- No definite or probable scaffold thrombosis was observed with DREAMS 2G tested in BIOSOLVE-II or any of it`s precursor devices tested in PROGRESS and BIOSOLVE-I in a total of 232 subjects

Back-up slides

BIOSOLVE-II

Baseline Characteristics & Lesion Location

N=123

Baseline Characteristics	N (%)
Age (mean ± SD)	65.2±10.3
Male	78 (63.4)
Hypertension	101 (82.1)
Hyperlipidemia	74 (60.2)
Smoking	67 (54.5)
Diabetes mellitus	36 (29.3)
Insulin dependent	11 (30.6)
Non-Insulin dependent	25 (69.4)
History of MI	29 (23.6)
Previous percutaneous Intervention	44 (35.8)

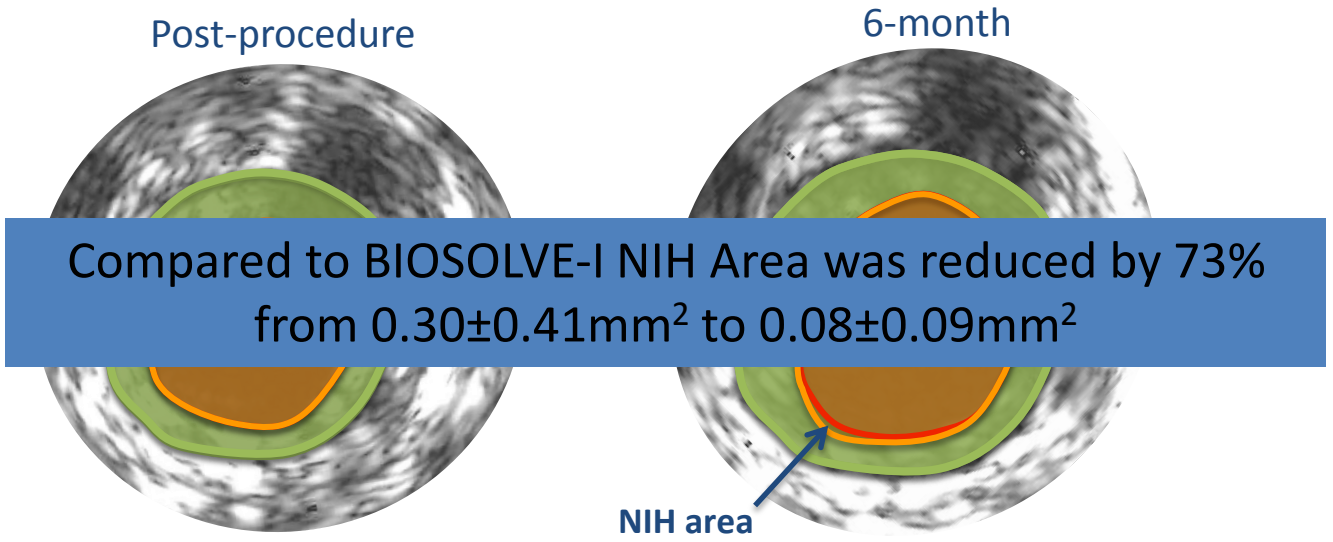
Lesion Location	N (%)
LAD	47 (38.2)
LCx	29 (23.6)
RCA	45 (36.6)
Intermediate Branch	2 (1.6)

Lesion Characteristics	N (%)
Lesion Length (mm ± SD)	12.61 ± 4.53
RVD (mm ± SD)	2.68 ± 0.40
AHA/ ACC Lesion Class B2/C	53 (43.8)
Calcification Moderate/Severe	13 (10.6)

BIOSOLVE-II

IVUS Analysis

Subgroup N=30



Compared to BIOSOLVE-I NIH Area was reduced by 73% from 0.30±0.41mm² to 0.08±0.09mm²

Lumen area

Scaffold Area

Vessel area

Plaque area

NIH= Neointimal Hyperplasia

	Post-procedure	**6-month**	**Δ6-month vs post [95% CI]**	**p-value**
Vessel area (mm²)	14.06±3.17	14.21±3.14	0.15[-0.13-0.42]	0.289
Scaffold area (mm²)	6.24±1.15	6.21±1.22	-0.03[-0.29-023]	0.803
Plaque area (mm²)	7.76±2.41	8.06±2.23	0.29[0.11-0.47]	0.002
NIH area (mm²)	NA	0.08±0.09	NA	NA

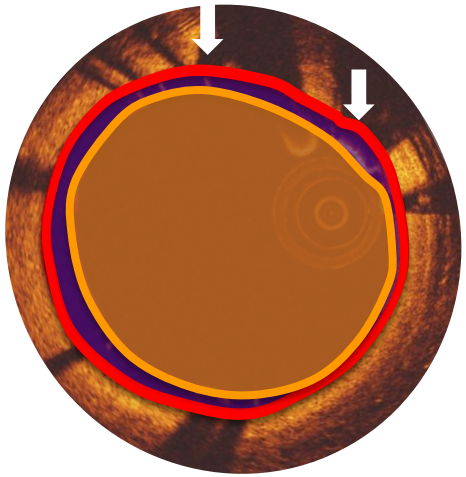
NA = Not Applicable

BIOSOLVE-II

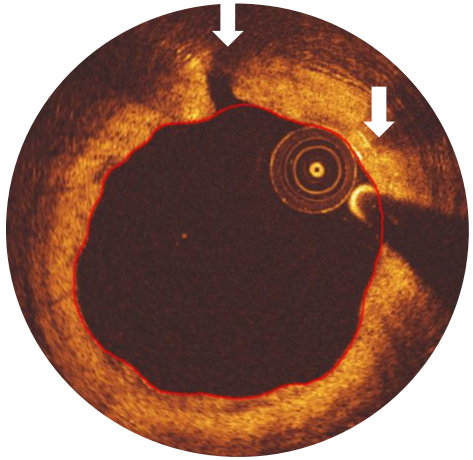
OCT Analysis

Subgroup N=30

Post-procedure



6-month



Scaffold Area

Lumen area

ISA area

	Post-procedure
Mean ISA area (mm^2)	0.16±0.16
Mean intraluminal mass area (mm^2)*	0.00±0.00

*Intraluminal mass is defined as a defect free from the vessel wall

ISA = Incomplete Strut Apposition

BIOSOLVE-II

Comparison of clinical results in PROGRESS, BIOSOLVE-I and BIOSOLVE-II

Clinical results at 6-month (4-month for PROGRESS)

	PROGRESS N=63	BIOSOLVE-I N=46	BIOSOLVE-II N=123
TLF[1] (%)	23.8	4.3	3.3
Cardiac Death (%)	0.0	0.0	0.8
Target Vessel MI (%)	0.0	0.0	0.8
Clinically driven TLR (%)	23.8	4.3	1.7
CABG	0.0	0.0	0.0
Scaffold Thrombosis Definite or probable	0.0	0.0	0.0

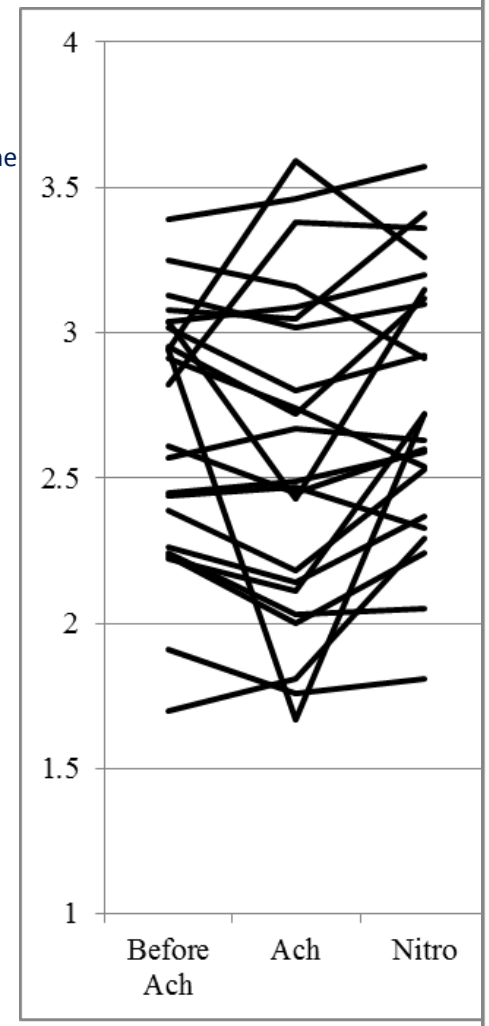
1. Composite of cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization and CABG

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

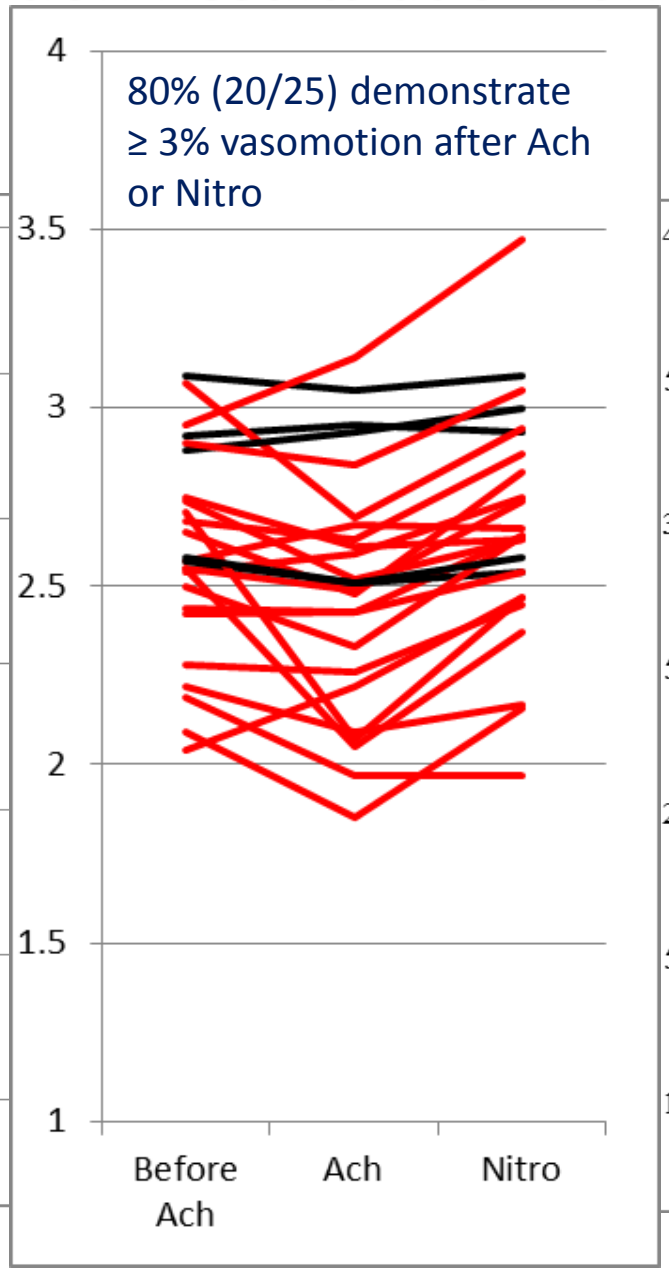
BIOSOLVE-II

Vasomotion Results at 6-month (N=25)

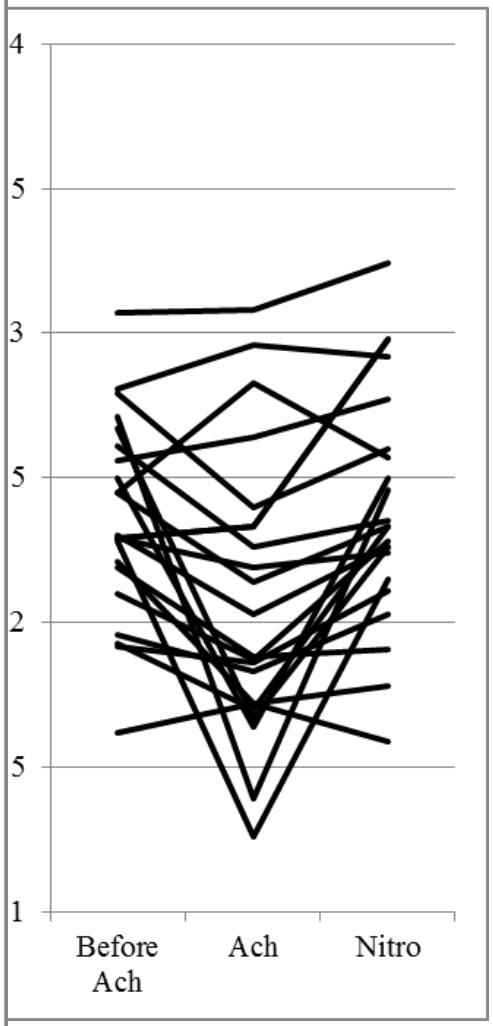
Mean Lumen Diameter
Proximal
(mm±SD)



80% (20/25) demonstrate ≥ 3% vasomotion after Ach or Nitro



Mean Lumen Diameter
Distal
(mm±SD)

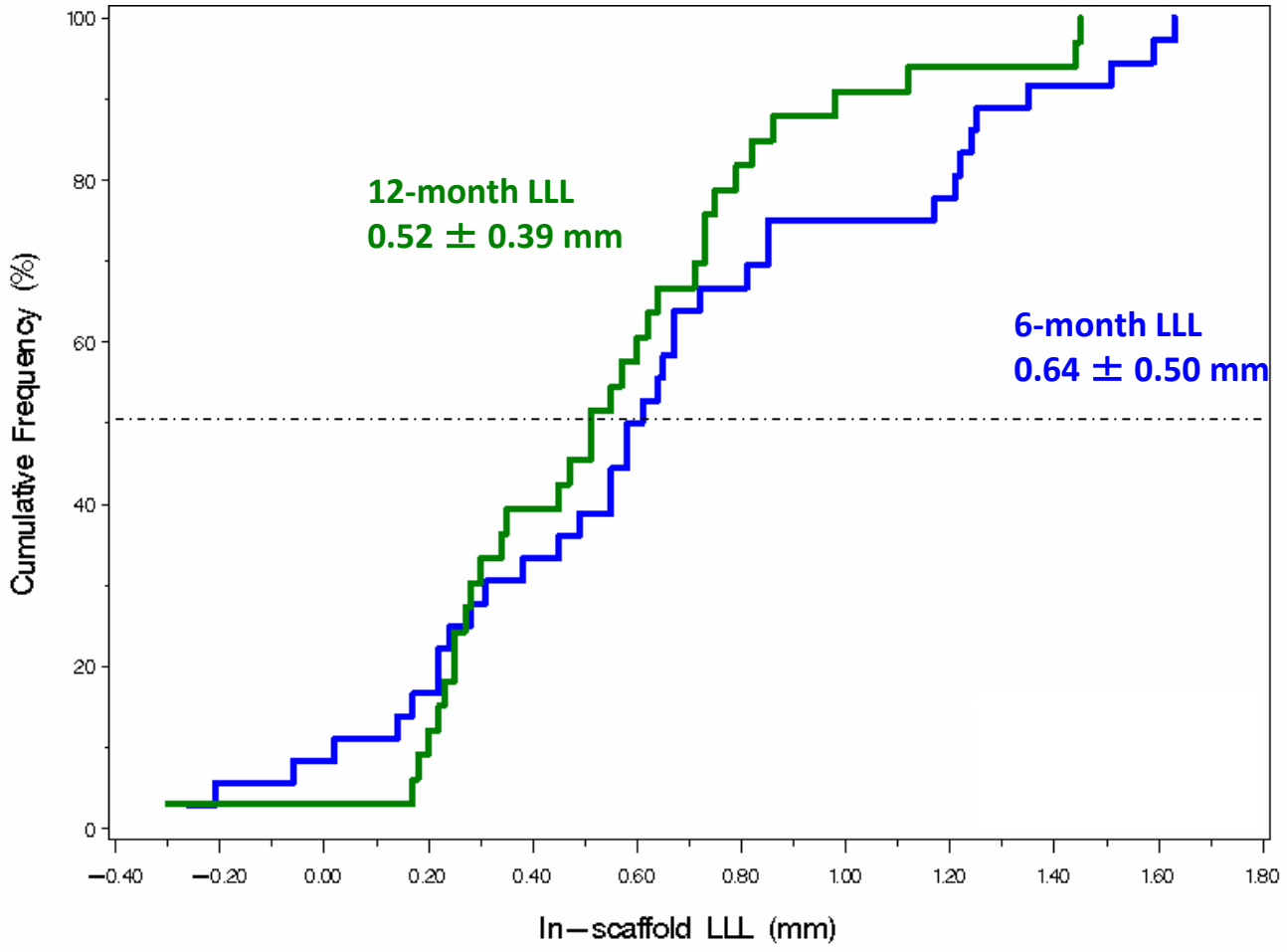


Ach = Acetylcholine

Nitro = Nitroglycerine

BIOSOLVE-I

BIOSOLVE-I study results
6-and 12-month late lumen loss (LLL)



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

Main take away

Very safe device

- No definite nor probable scaffold thrombosis
- Also no ST in PROGRESS and BIOSOLVE-I (total n=232 patients)

Optimal scaffolding time

- Vasomotion was already demonstrated at 6 months(>80 % positive responders at 6m)
- True bioresorbable scaffold offering support and then uncaging of the vessel wall

Excellent clinical profile

- Low TLF (Target Lesion Failure) 3.3 % and low TV-MI (Target Vessel Myocardial Infarction) at 0.8 % (none out of hospital)

Conclusion: Based on the clinical outcomes of BIOSOLVE-II, the BIOTRONIK Magnesium Scaffold is a viable alternative to polymeric scaffolds.