Update on the drug-eluting magnesium absorbable scaffold: Two-year results from the BIOSOLVE trial

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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	• Volcano • Medtronic Vascular • Abbott Vascular • Boston Scientific
• Consulting Fees/Honoraria	• Biotronik • Medtronic • Abbott Vascular • Boston Scientific • Lilly Daiichi • Astra Zeneca

Rationale for Bioabsorbable Metallic Scaffold

- Metallic stents has a temporary mechanical role in the treatment of coronary artery disease.
- Bioabsorbable scaffolds temporarily support the vessel and additionally can release a drug similar to a permanent DES.
- After absorption no permanent scaffolding structures remain in the vessel wall allowing to resume its natural physiology.
- This may reduce the risk of late and very late thrombotic events and provide the option for reducing long-term dual antiplatelet therapy
- In addition, non-invasive imaging of the scaffolded vessel lumen with CT or MRI should become possible
- Biotronik has developed an absorbable metal scaffold (AMS) made of a magnesium alloy
- Magnesium alloy has a similar radial force to cobalt chrmium stent feels like metallic stent and bioabsorbed within 6-12 m

AMS device evolution

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%

Source: R Erbel, et al. The Lancet. 2 June 2007: 369 (9576): 1869-1875.

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

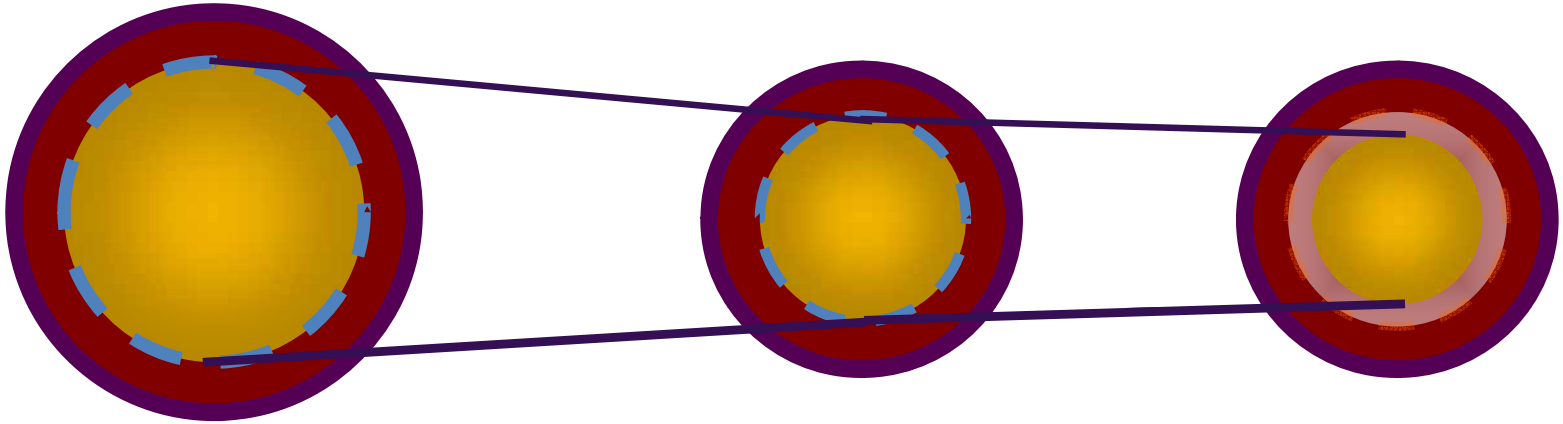
- Device was safe/feasible
- Effectiveness required optimization
- IVUS findings showed lumen loss was due to loss of scaffolding area and NIH
- No additional safety concerns between 12 months and 7 years

PROGRESS-AMS

Lessons learned from PROGRESS study

PROGRESS-I showed safety and feasibility

Post implantation **4-month follow-up**



Contribution to lumen loss

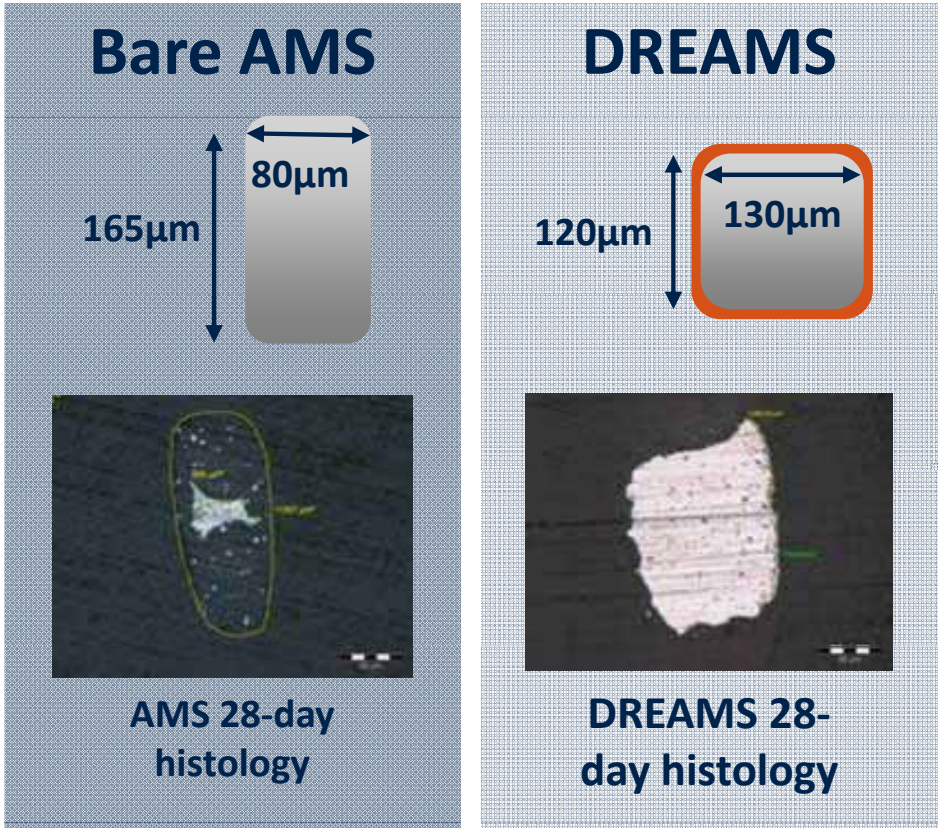
Loss of scaffold area	In-stent neointima
53%	47%

Results of PROGRESS* (AMS I FIM): LLL 1.08 mm; TLR 23.8%

Optimization of device with <u>prolonged scaffolding time</u> and an <u>anti-proliferative drug</u>

* Erbel R. et al., Lancet 2007;369:1869-75,
Waksman et.al, JACC Cardiovasc Interv 2009;2:312-320

DREAMS device evolution



DRug-Eluting AMS (DREAMS)

- Refined alloy with slower absorption rate
- Reduced strut thickness
- 6-crown design
- PLGA polymer carrier
- Paclitaxel drug elution
- Used in BIOSOLVE-I study

BIOSOLVE-I

BIOSOLVE-I study design

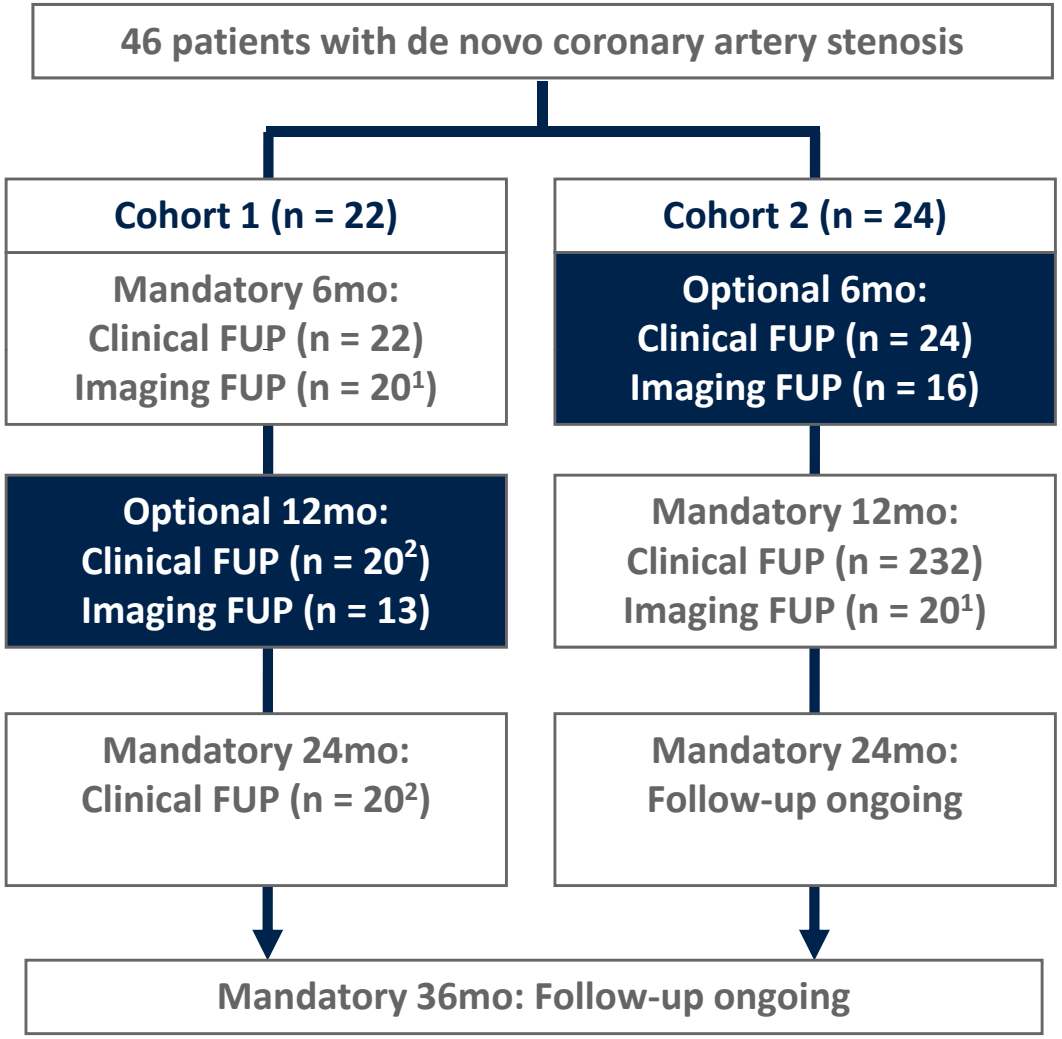
BIOSOLVE-I

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] A total of 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)



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

BIOSOLVE-I study results

Six to 24-month clinical follow-up

BIOSOLVE-I

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

Clinical results	6-month	12-months	24-months
	Cohort 1 & 2	Cohort 1 & 2	Cohort 1
TLF	4.3% (2/46)	7.0% (3/43)	10.0% (2/20)
Cardiac death	0.0%	0.0%	0.0%
MI[1]	0.0%	2.3% (1/43)	0.0%
Scaffold thrombosis	0.0%	0.0%	0.0%
TLR (clinically driven)[2]	4.3% (2/46)	4.7% (2/43)	10.0% (2/20)

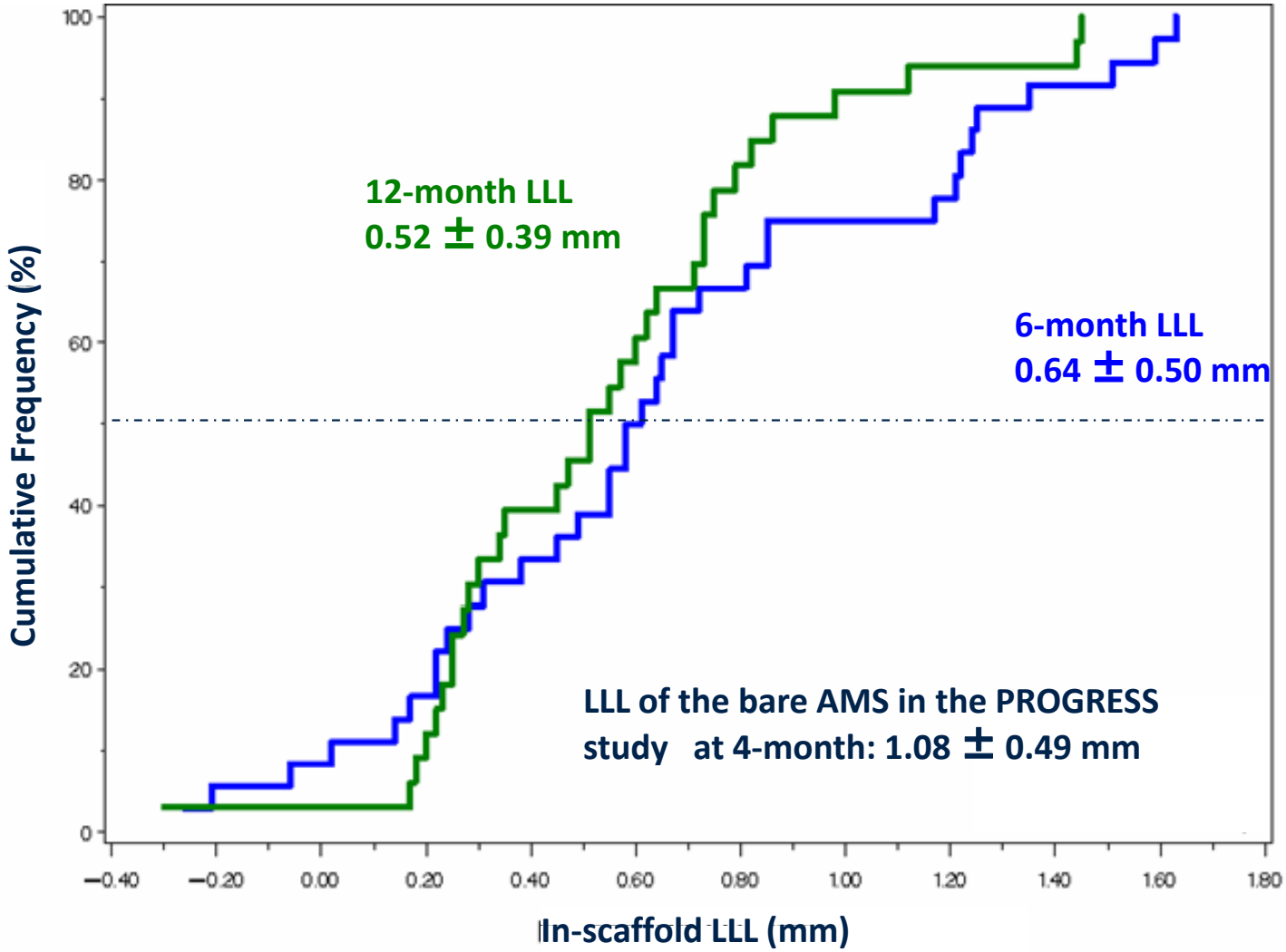
Device Success: successful delivery of the scaffold to the target lesion, appropriate deployment, successful removal of delivery system.
Procedure Success: device success plus attainment of a final residual stenosis of <50% of the target lesion, absence of MACE during the hospital stay up to 7 days.

[1] Target vessel peri-procedural MI (DREAMS was implanted in the OM, MI occurred in the LCx)
[2] TLR occurred during 6M FUP, both pts had angina, 1 pt received an additional DREAMS in the target lesion during the initial procedure because of a flow-limiting bailout situation

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

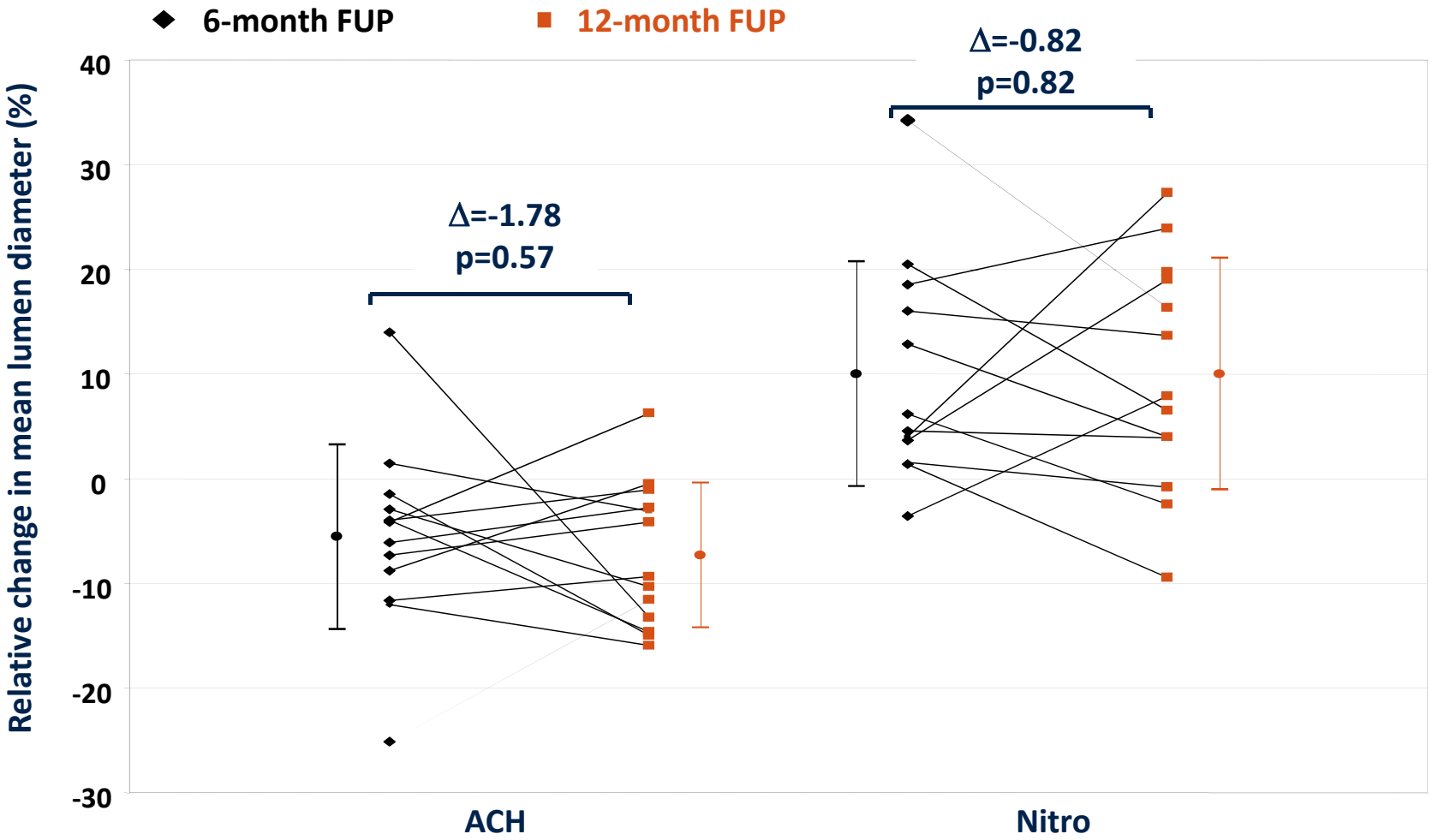
BIOSOLVE-I study results

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



BIOSOLVE-I study results

Change in vasomotion between 6- and 12-month (N=13) In-Scaffold

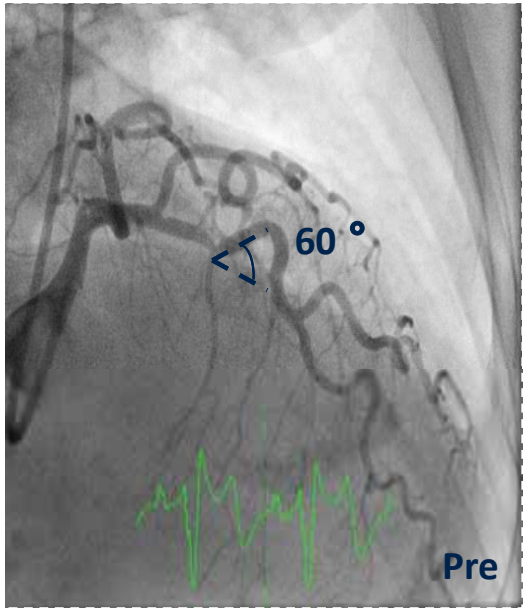


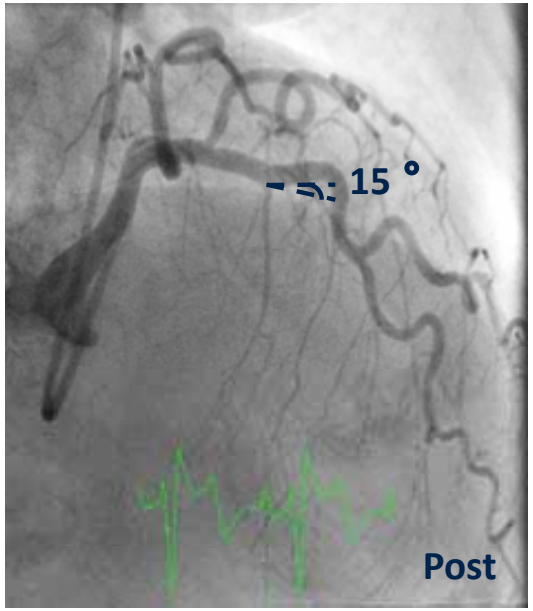
Acetylcholine (ACH): Presents the % change in mean lumen diameter between pre-and post ACH at the highest response

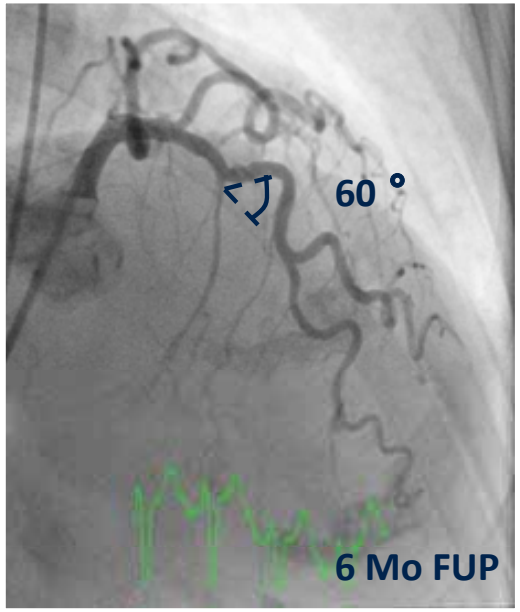
Nitroglycerine (NTG): Presents the % change in mean lumen diameter between post-ACH and Nitro

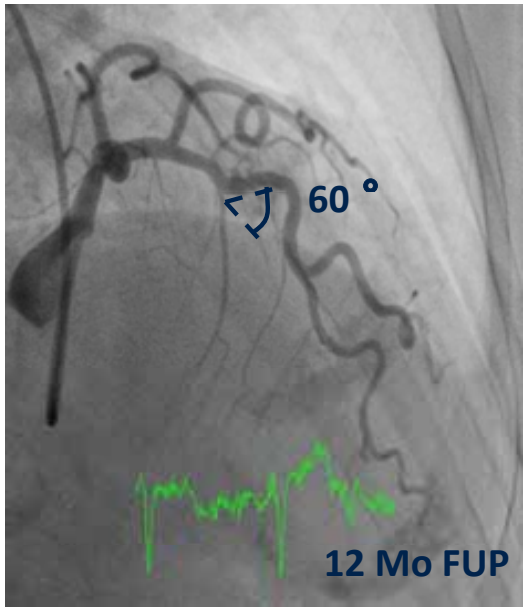
BIOSOLVE-I study results

Vessel angulation







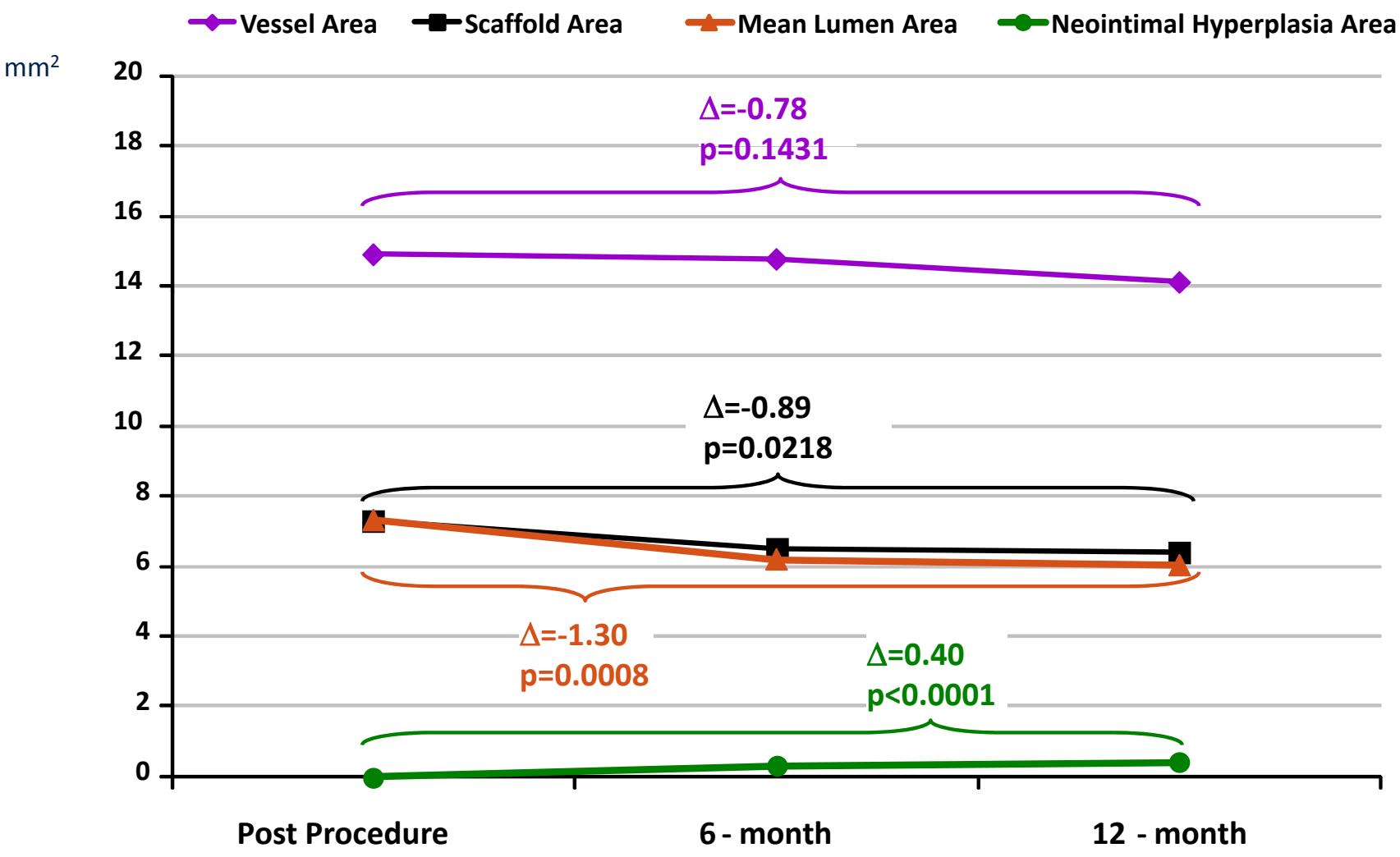


	Pre-Procedure N=47	Post-Procedure N=47	6-Month FUP N=36	12-Month FUP N=34
Lesion Angulation (°)	31.38 ± 21.23	14.89 ± 12.00	26.11 ± 15.91	30.88 ± 18.81
		Post vs. 6-Mo.	**Post vs. 12-Mo.**	**6-Mo.vs. 12-Mo.**
P-value		<0.0001	<0.0001	0.020

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

BIOSOLVE-I study results

IVUS results up to 12-month (N=21)

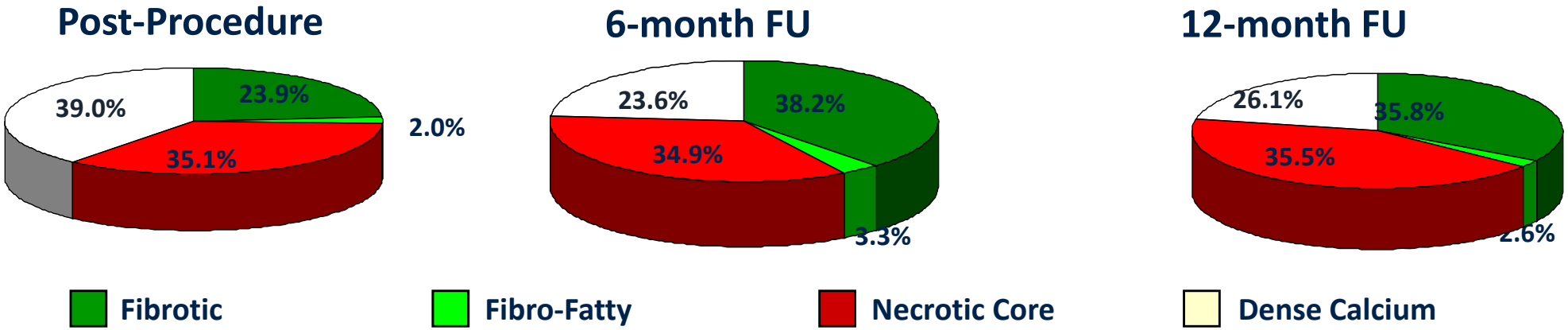


Source: M Haude, et al. Lancet 2013; 381:836-44.

BIOSOLVE-I study results

IVUS VH Analysis up to 12-month

BIOSOLVE-I

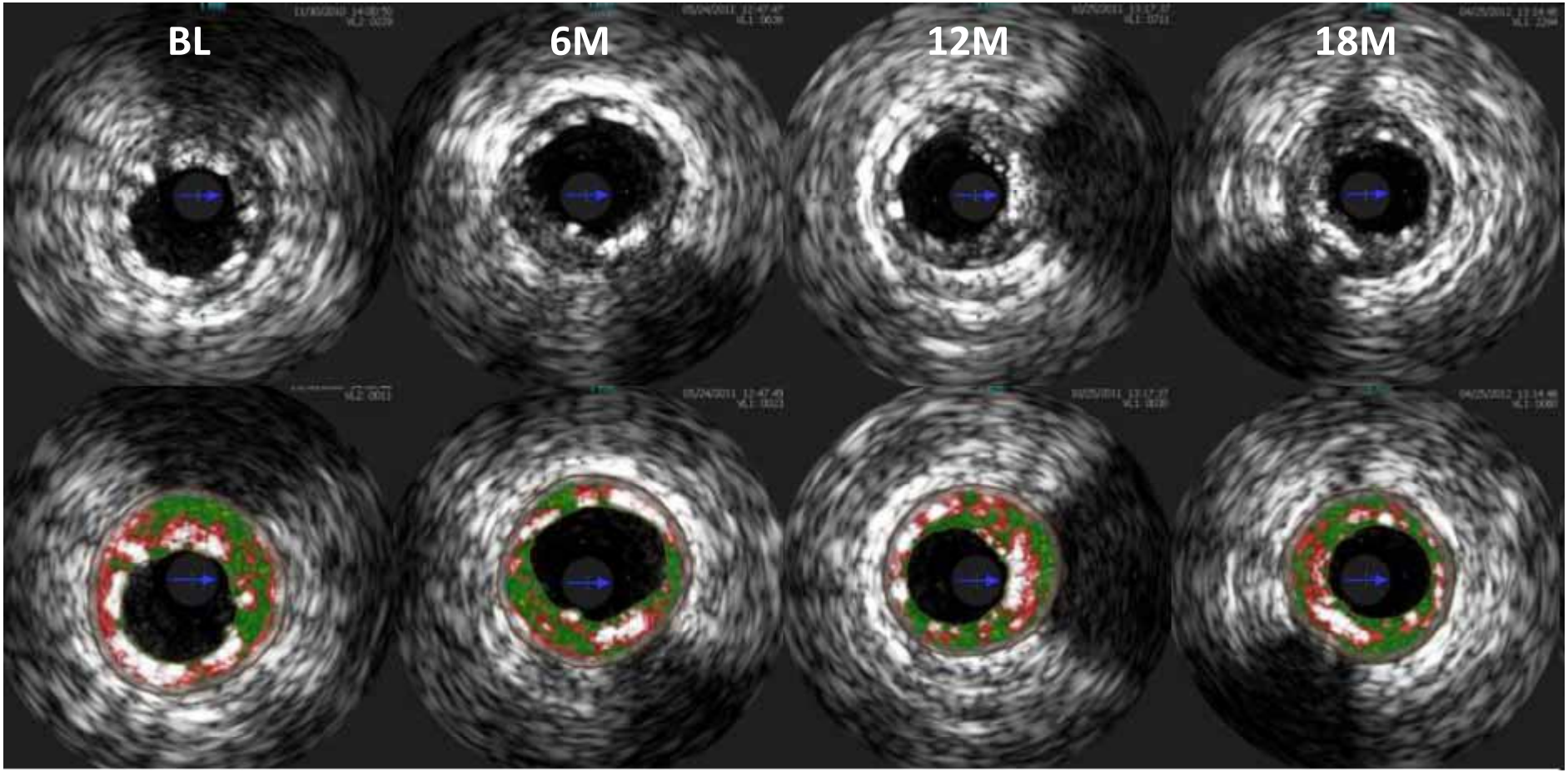


N=9 scaffolds

	Δ 6-month vs post-procedure	p-value	Δ 12-month vs 6-month	p-value
Dense calcium area (%)	-15.41±9.83 (-21.83;8.99)	0.0015	2.48±2.47 (0.87;4.09)	0.0166
Necrotic core area (%)	0.19±3.43 (-2.43;2.06)	0.8700	0.60±2.96 (1.33;2.54)	0.5600
Fibro fatty area (%)	1.31±1.94 (0.04;2.59)	0.0779	-0.73±0.70 (-1.19;-0.27)	0.0140
Fibrous area (%)	14.29±8.63 (8.65;19.92)	0.0011	-2.35±4.33 (-5.18;-0.48)	0.1400

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

GER-443-015 IVUS-VH Results

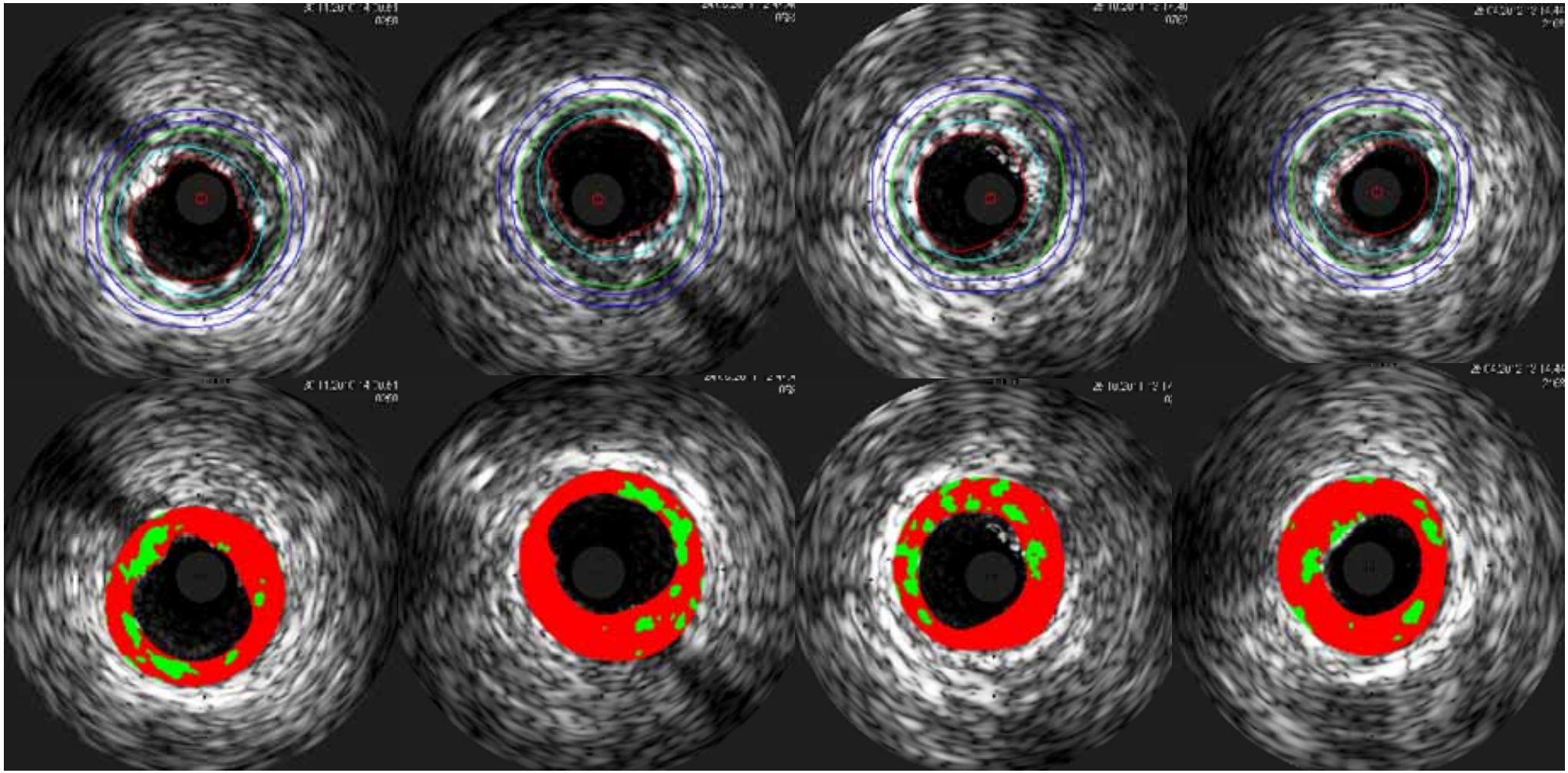


	BL	6M	12M	18M
DC (%)	41.76	24.46	29.86	29.97
NC (%)	36.23	38.44	37.69	38.63
FF (%)	0.82	3.26	2.55	2.41
FI (%)	21.19	33.83	29.90	28.98

GER-443-015 IVUS Echogenicity

Quantitative Analysis % Hyperechogenicity

BL	6M	12M	18M



31%	18%	21%	19%

BIOSOLVE-I

BIOSOLVE-I study results

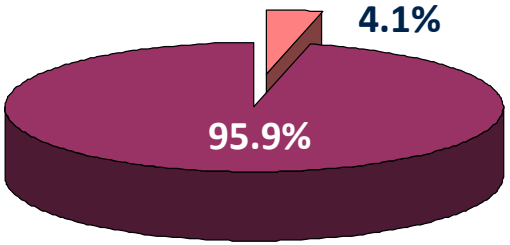
Serial assessment of OCT results

	Post-procedure N=7	6-month N=7	12-month N=7	p-value post vs. 6-month	p-value 6 vs.12-month
Discernible struts	5791	4962	3540	0.1179	0.0050
Mean lumen area (mm^2)	7.90±1.24	5.70±0.99	5.34±1.14	<0.0001	0.040
Mean scaffold area (mm^2)	7.94±1.29	6.79±1.51	6.49±1.52	0.0058	0.2149
Neo-intima area (mm^2)	0.00±0.00	1.55±0.51	1.58±0.34	0.0002	0.7943
Neo-intima area (%)	0.00±0.00	23.91±8.22	25.51±5.40	0.0003	0.2800
Minimal Thickness (mm)	N/A	0.09±0.04	0.10 ±0.04	N/A	0.1280
Maximal Thickness (mm)	N/A	0.32±0.05	0.30±0.04	N/A	0.1992

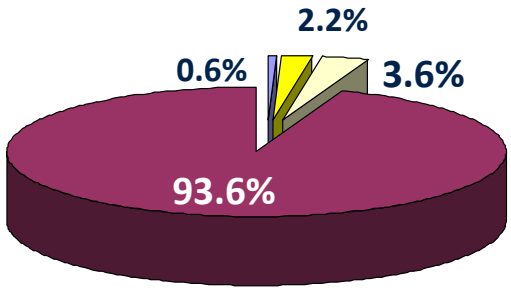
BIOSOLVE-I study results

OCT assessment of strut apposition

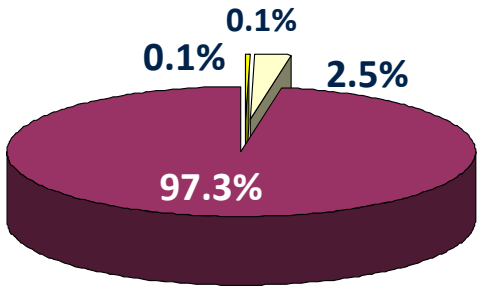
Baseline



6-month FUP

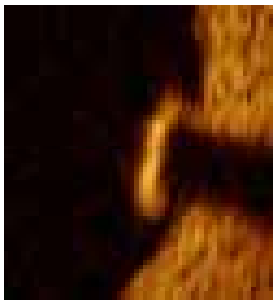


12-month FUP

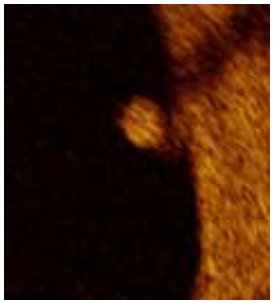


Apposed | ISA | Late Acquired ISA | Persistent ISA | Resolved ISA

N=7 scaffolds, 5.791 struts



Apposed



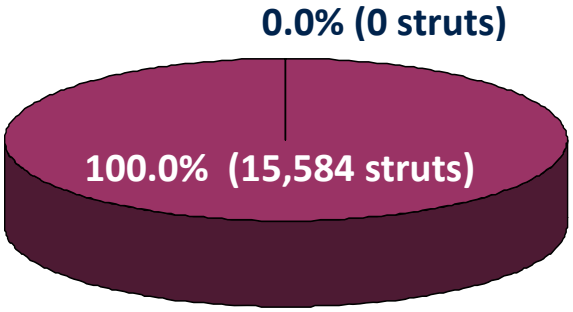
ISA – Incomplete Strut Apposition

BIOSOLVE-I

BIOSOLVE-I study results

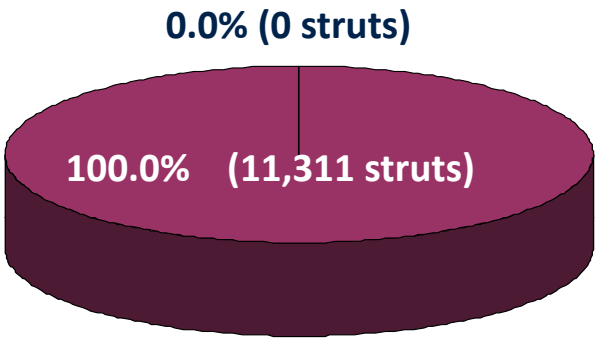
OCT assessment of strut coverage

6-month follow-up



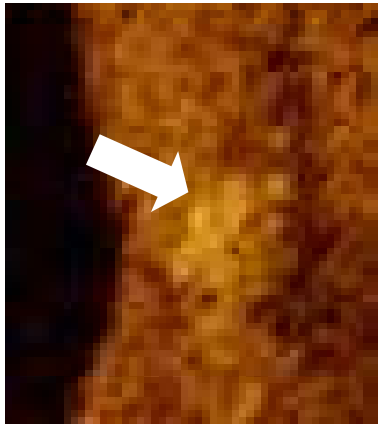
N=27 scaffolds, 15.584 struts

12- month follow-up



N=21 scaffolds, 11.311 struts

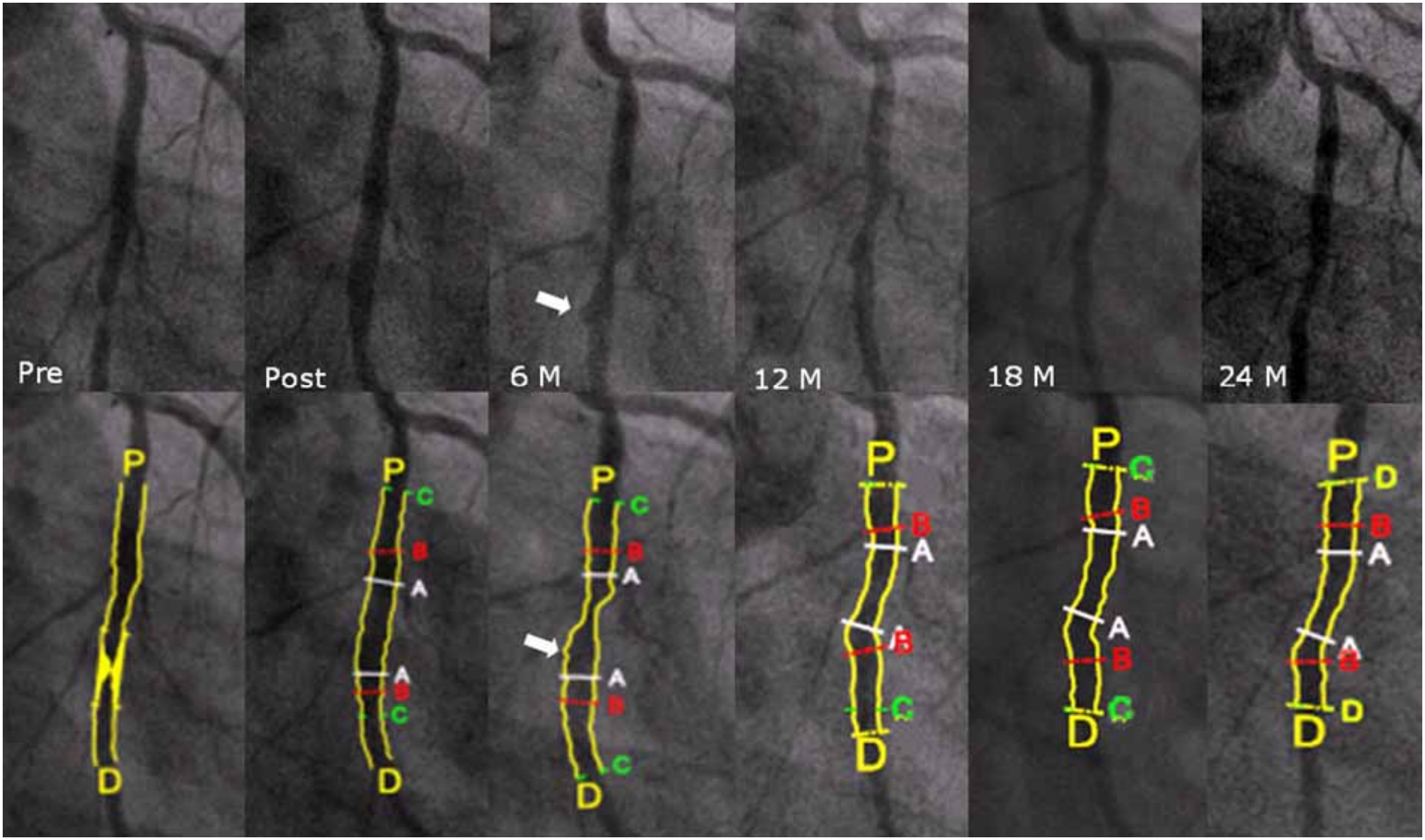
Complete Incomplete



Complete

BIOSOLVE-I

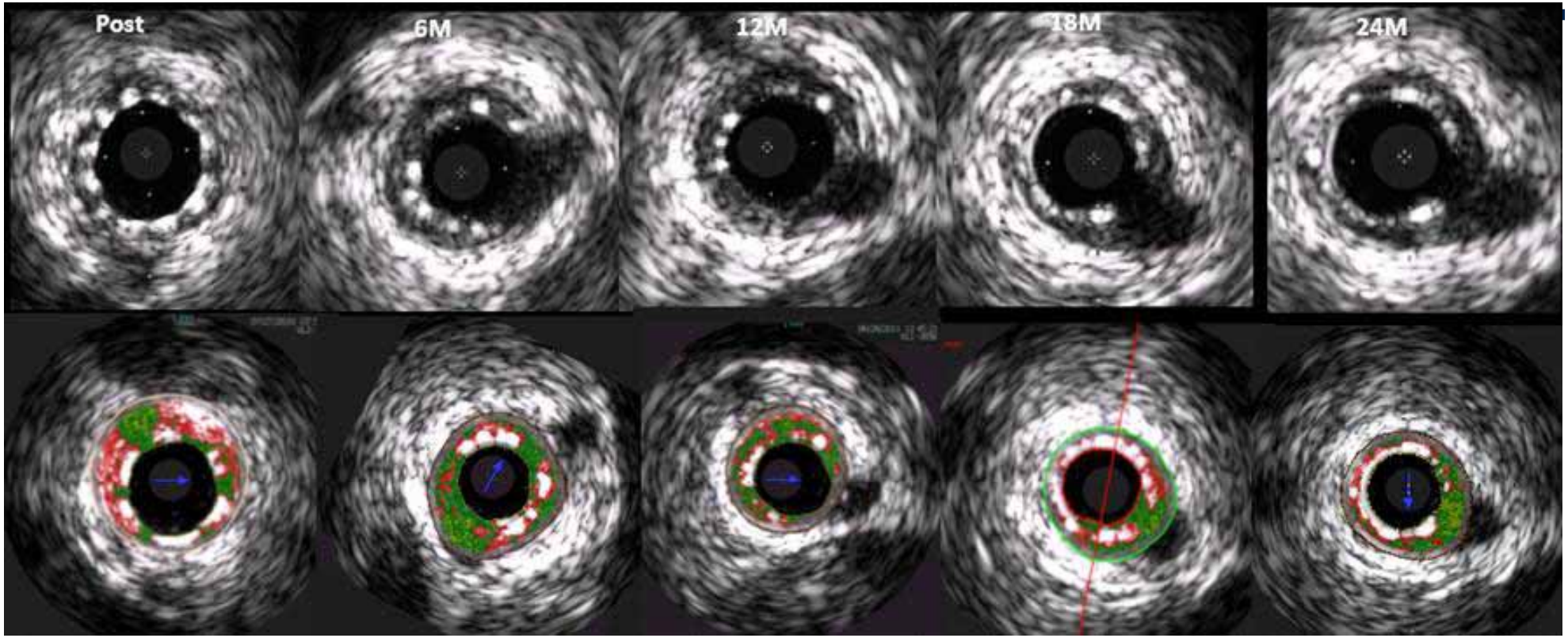
Case Presentation GER443-001



RVD (mm)	2.22	2.26	2.36	2.68	2.54	2.46
MLD (mm)	0.52	2.36	1.11	2.13	2.02	1.86
DS (%)	76.8	7.6	54.6	21.1	20.2	23.9
LLL (mm)	NA	NA	1.25	0.23	0.34	0.50

Case Presentation GER-443-001

Greyscale and VH IVUS based on mean lumen area

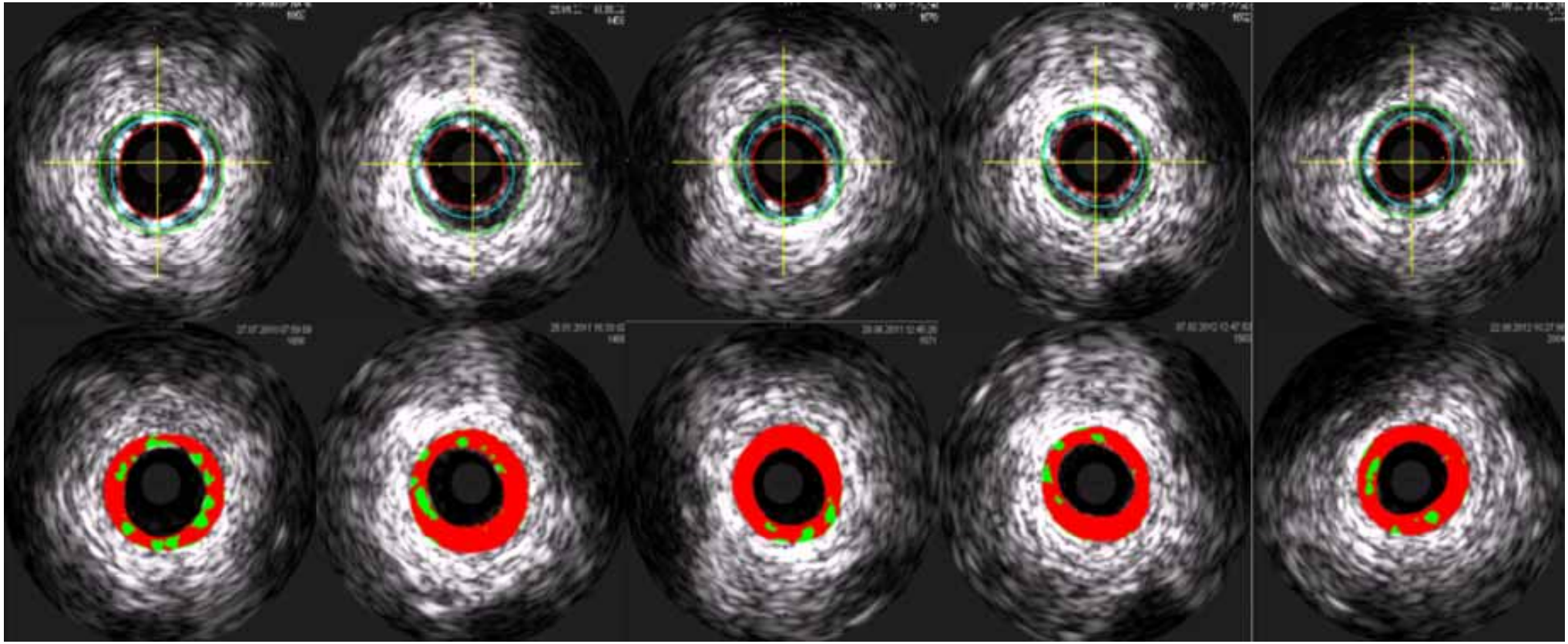


VA (mm^2)	8.32	13.69	12.21	9.97	10.26
LA (mm^2)	5.04	5.78	5.53	4.16	3.52
SA (mm^2)	5.04	7.01	6.11	5.19	5.14
DC (%)	33.35	20.63	21.65	26.99	24.00
NC (%)	39.13	26.04	34.85	27.94	31.46
FF (%)	2.60	3.33	2.91	3.12	2.60
FI (%)	24.92	40.00	40.60	41.95	41.94

Case Presentation GER-443-001

Echogenicity

Post	6M	12M	18M	24M



1.25	0.70	0.50	0.42	0.51

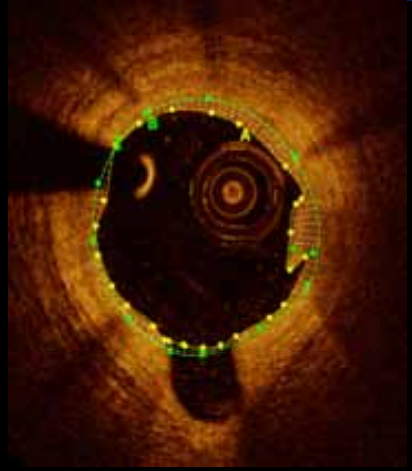
Hyperechogenic area [mm^2]

Green = Hyperechogenic tissue components including scaffold struts

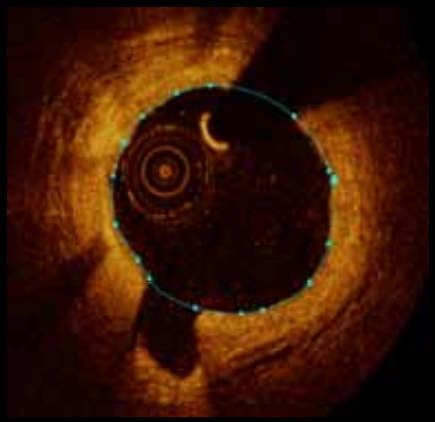
Red = Hypoechogenic tissue components

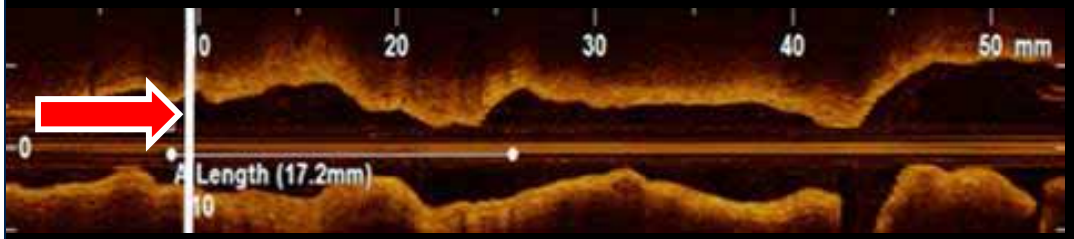
BIOSOLVE-I

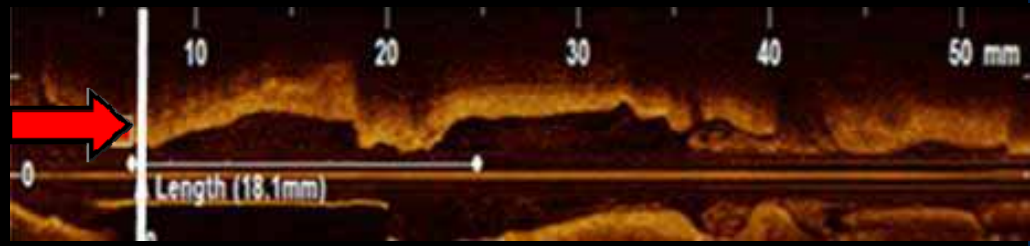
6 MONTHS
In-Scaffold lumen area
Cross Section: 4.02 mm²
Mean: 4.26 mm²
Minimal: 1.91 mm²



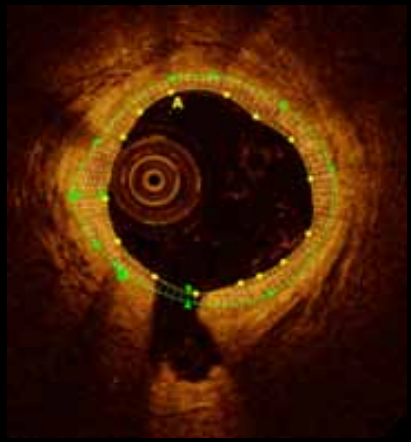
12 MONTHS
In-Scaffold lumen area
Cross Section: 4.30 mm²
Mean: 4.10 mm²
Minimal: 2.17 mm²



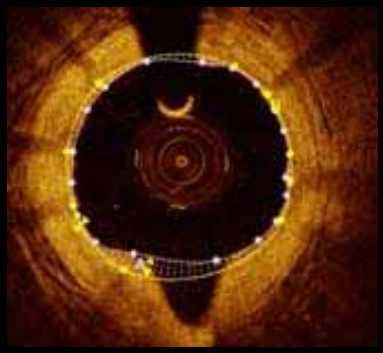


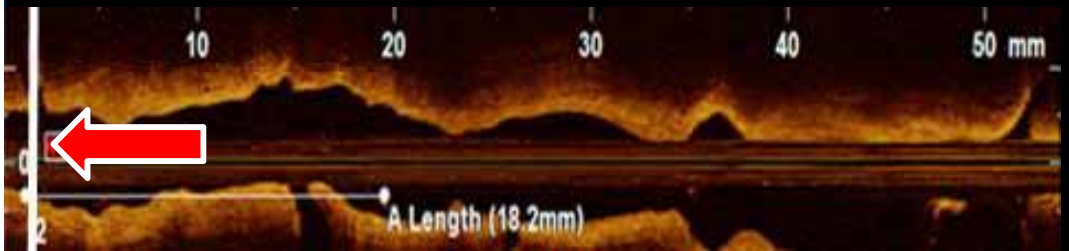


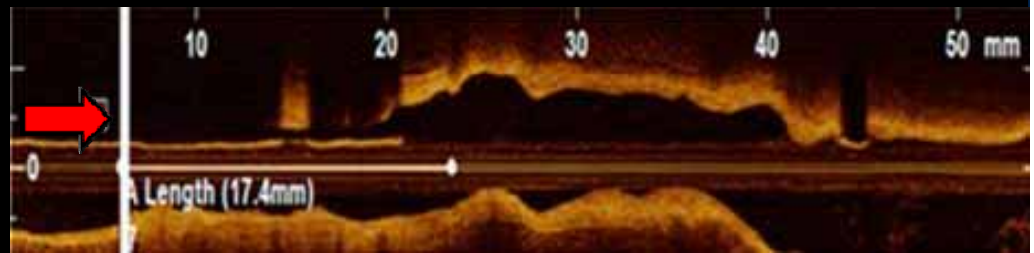
18 MONTHS
In-Scaffold lumen area
Cross Section: 3.36 mm²
Mean: 3.21 mm²
Minimal: 2.01 mm²



24 MONTHS
In-Scaffold lumen area
Cross Section: 3.62 mm²
Mean: 3.06 mm²
Minimal: 2.04 mm²





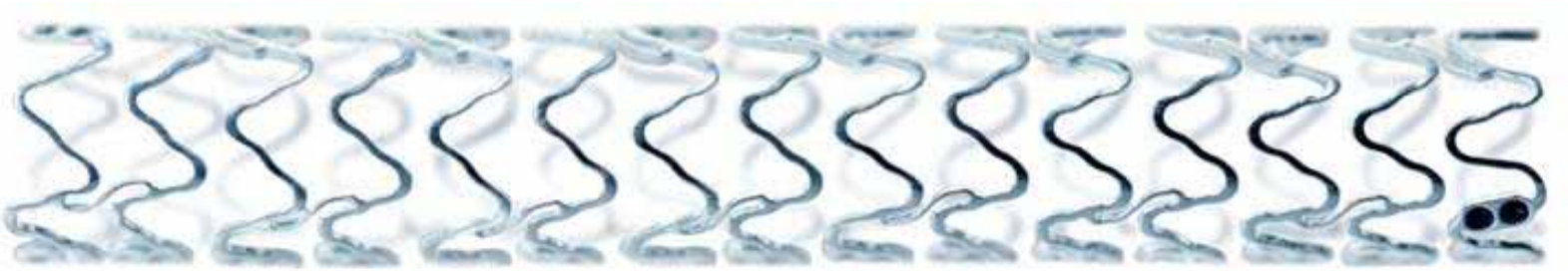


Conclusions

- DREAMS demonstrates an excellent safety profile up to 24 months
- TLF rate remains stable up to 24-month follow-up
- DREAMS demonstrated significantly improved efficacy at 12 months compared to the bare AMS:
  - Reduction in LLL of 61% compared to the 4-month data of the bare AMS (1.08mm vs. 0.52mm)
  - Reduction of TLR rate by 82% (26.7% vs. 4.7%)
- BIOSOLVE-I confirms that vascular restoration is achieved with the return of vasomotion and vessel angulation at 6-month follow-up with no further reduction in dense calcium between 6 to 12 months

DREAMS program outlook

- New scaffold design will increase post-dilatation capabilities
- Markers will be added to the device to increase radiopacity
- Preclinical studies are underway with a Limus drug
- BIOSOLVE-II planning is underway and will commence later this year, pending preclinical results of DREAMS 2nd generation



DREAMS 2nd Generation Design Overview

Scaffold Backbone

– Bioabsorbable Magnesium alloy

– 150µm strut thickness

Base coating

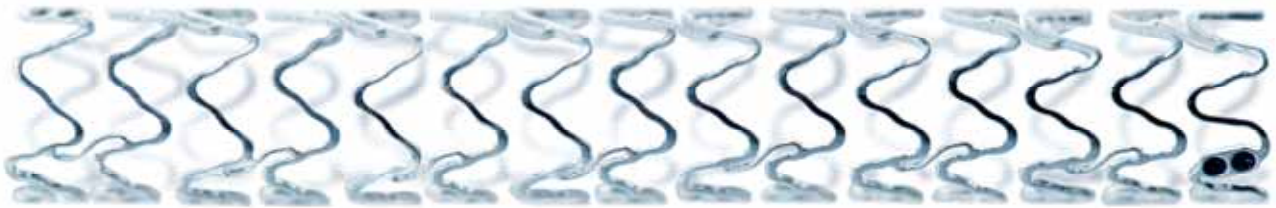
– Bioabsorbable polymer

– Control of degradation

Drug coating

– Bioabsorbable polylactic acid polymer

– Sirolimus, 1.4µg/mm²



Delivery system

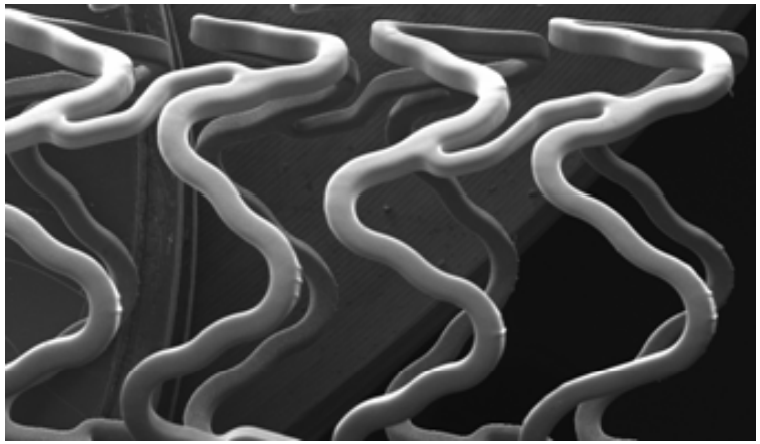
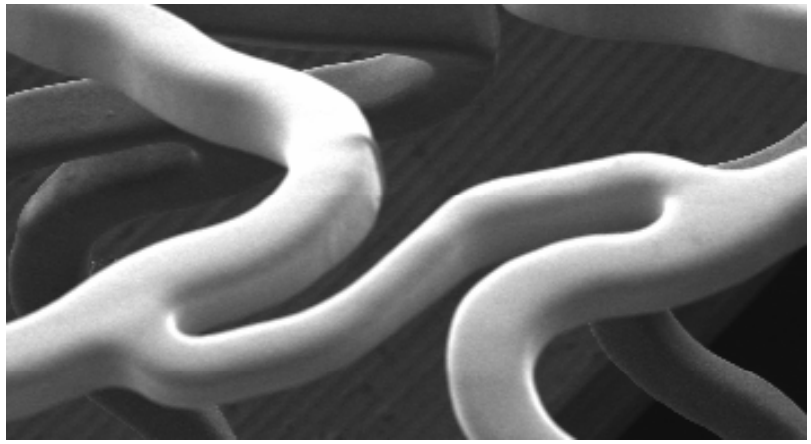
– RX catheter

– 6F compatible

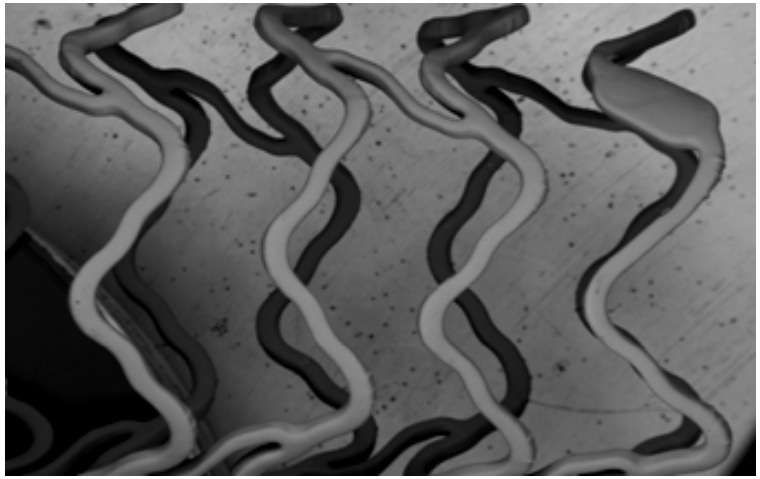
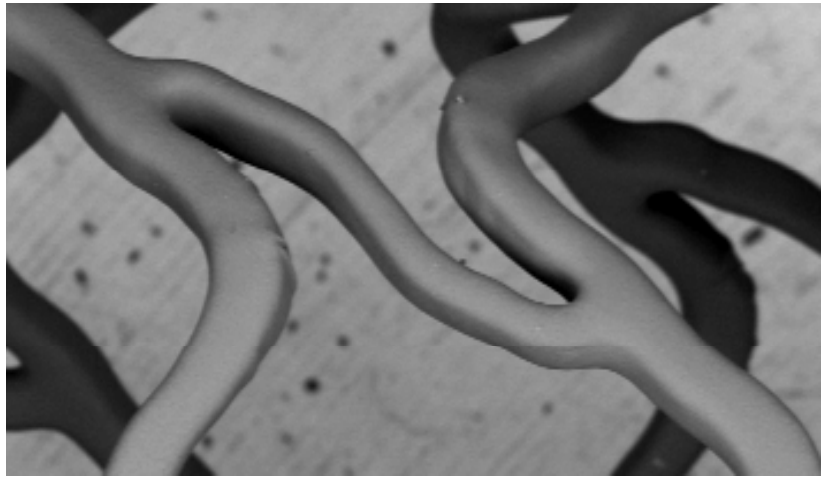
Radiopaque markers

– Tantalum compound

Coating integrity of DREAMS

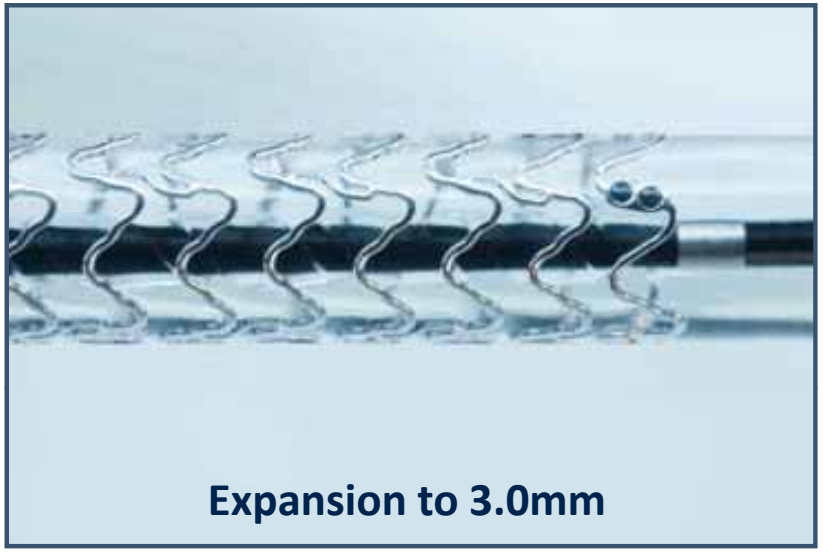
SEM images of expanded 3.0 mm DREAMS (expansion diameter 3.5 mm)

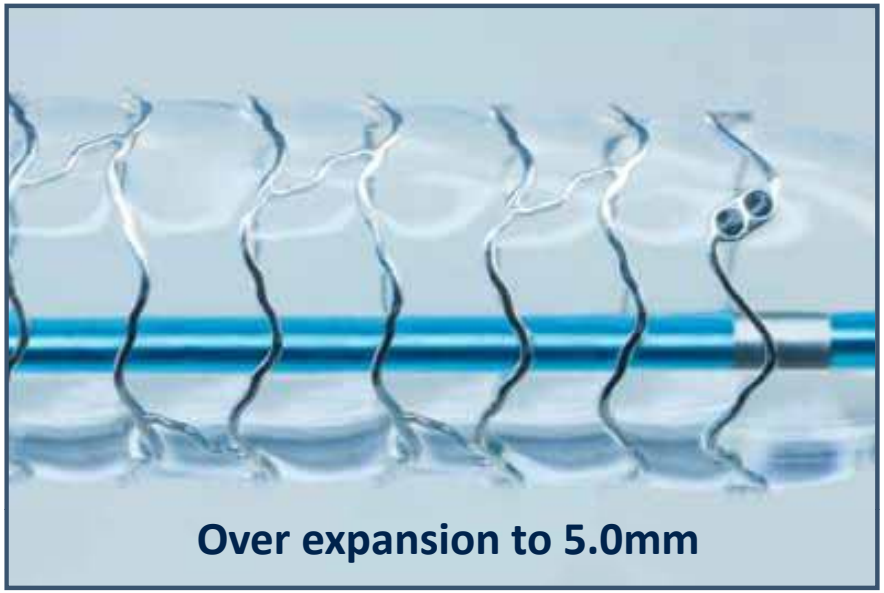
SEM images of expanded 3.0 mm DREAMS (expansion diameter 4.25 mm)

Post-dilatation capability of DREAMS scaffold

DREAMS crimped (3.0mm nominal)



Expansion to 3.0mm



Over expansion to 5.0mm