ANGIOPLASTY SUMMIT

TCTAP 2011

TRANSCATHETER CARDIOVASCULAR THERAPEUTICS ASIA PACIFIC

The Biotronik Bioabsorbable Magnesium Scaffold DREAMS

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Disclosures

- Consultant : Biotronik, Medtronic, Boston Scientific. Abbott Vascular
- Speaker Biotronik BSC, Medtronic, Abbott Vascular
- Research Grants: Biotronik, Medtronic, Boston Scientific. GSK, Medicine Company, Sanofi BMS

A scaffold is different from a stent

Drug Eluting Scaffold	Drug Eluting Stent
Temporary backbone	Permanent backbone
Degradable polymer coating	Permanent polymer coating
After elution period of about 3 months, the drug is completely gone	Elution time over 2 months, with possible remaining drug embedded in permanent polymers

- The mechanism of a temporary scaffold is different from a permanent stent.
- It fulfills a transient role in supporting the vessel and eluting a drug to inhibit neointimal hyperplasia.
- Permanent caging of the vessel is eliminated.
- After scaffold degradation, the vessel is returned to its natural functionality – no polymer or drug is left behind to cause inflammation.

Challenges With Bioabsorbable Stents

- Time of degradation
- Rate of degradation
- Biodegradable products
- Remaining polymer
- Biocompatibility
- Elution of the drug from biodegradable stents
- Scaffolding and radial force
- Recoil: early and late
- Radiopacity of the stents

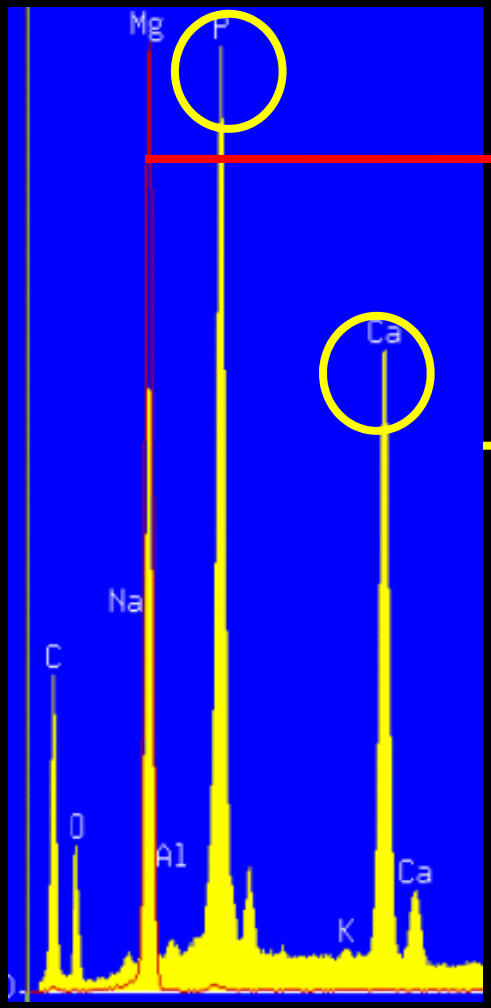
AMS is a metallic stent with favorable mechanical properties

- Design & Manufacturing
  - Based on Finite Element Analysis
  - Laser cut and polished surface
- Mechanical parameters
  - Low bending stiffness
  - Low crossing profile (1.2 mm)
  - Low recoil (<5%)
  - High radial strength (~1 bar)
- Clinical effects
  - Good trackability and device success rate of 99.4%*
  - Good stent apposition

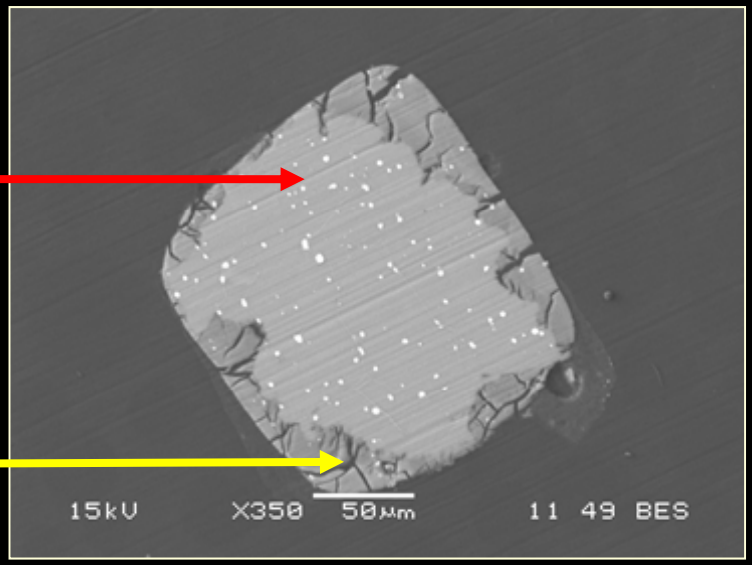
San Pellegrino:
Mg: 53.5 mg/l

* Analysis includes existing AMS-1 clinical data (BEST-BTK, INSIGHT, PROGRESS)

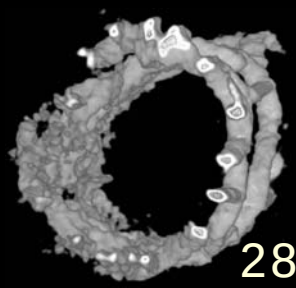
Analysis of degradation products by EDX analysis



Mg alloy before degradation



Conversion layer: soft shell of $Ca(PO_4)_2$

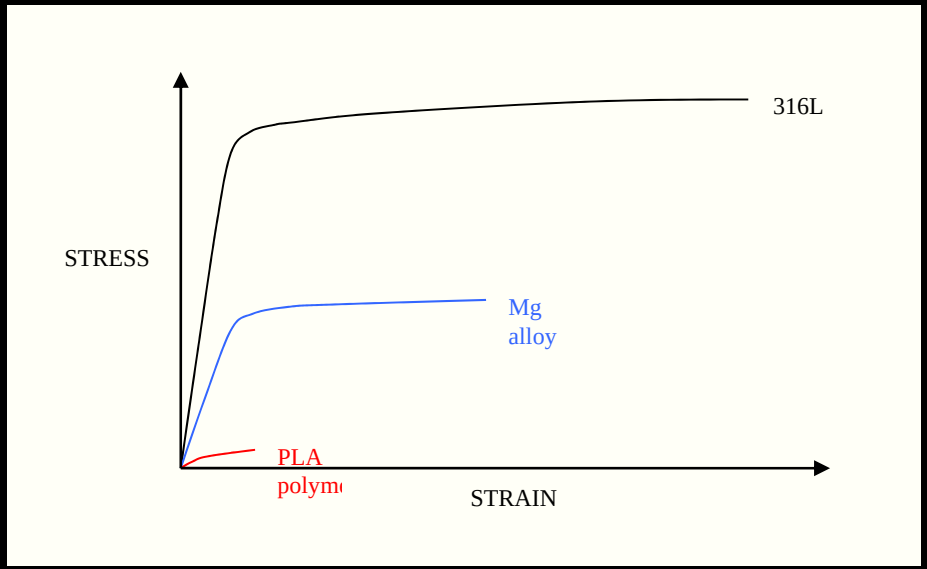


28 days in mini-pig

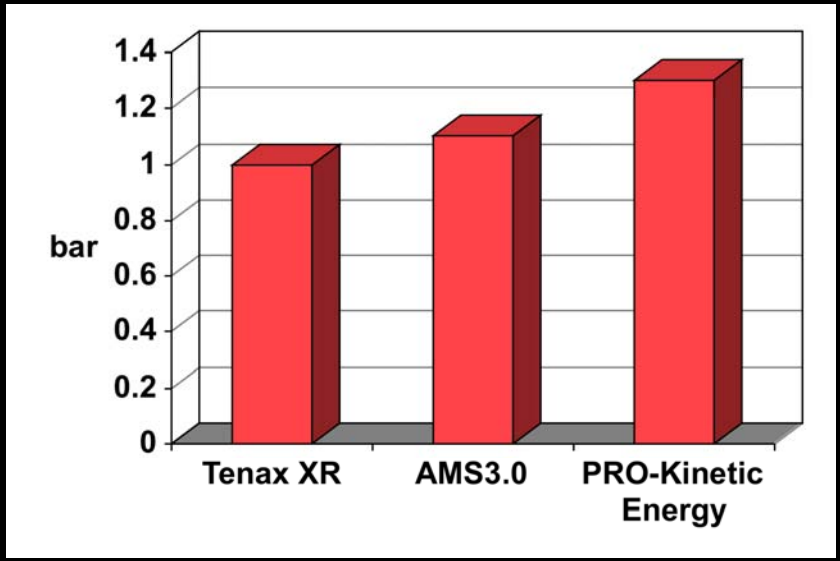
Mg alloy after 13 days in porcine blood

Acute mechanical properties of Mg alloys more favorable than that of polymers

Stress-Strain-Diagram



Collapse pressure

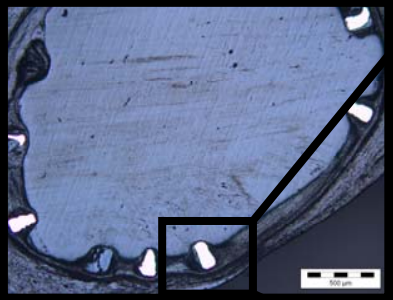


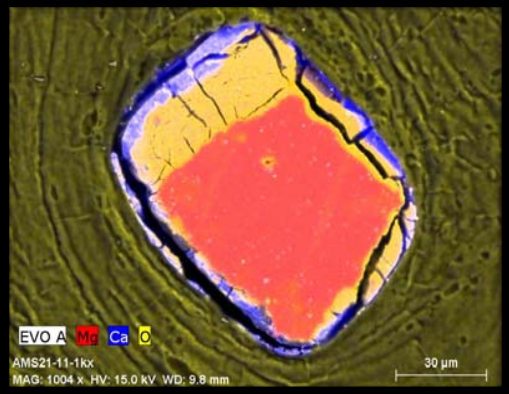
Theoretical strut section to obtain similar mechanical results:

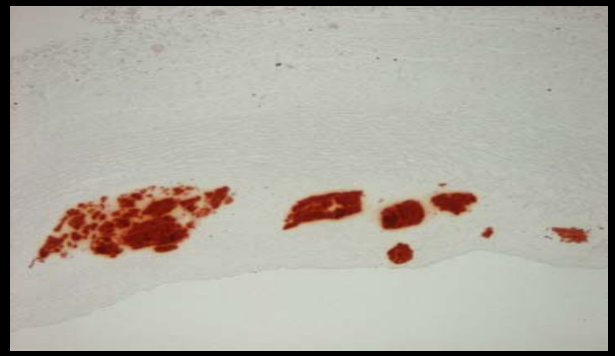
DREAMS: ~120µm
BVS: ~150µm

Degradation product composition in vivo

- Magnesium of the AMS scaffold is completely replaced with conversion products
- The polymeric drug coating is fully degraded
- Degradation process and conversion product composition in clinical and preclinical use is similar

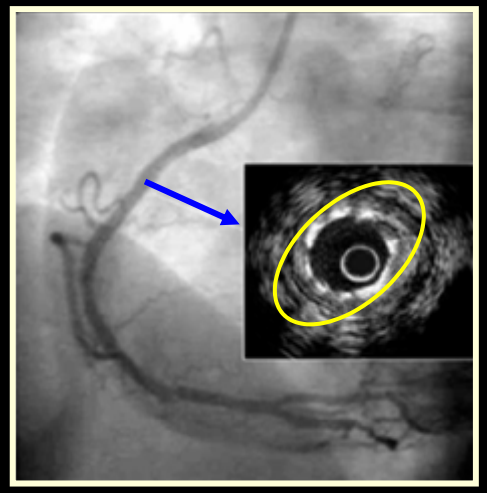






Sources: J. Riedmüller; Yucatan Minipig, 42 days FUP // Zartner P. First Successful Implantation of a Biodegradable Metal Stent Into the Left Pulmonary Artery of a Preterm Baby. Catheterization and Cardiovascular Interventions 66:590–594 (2005))

AMS allows non-invasive imaging of the stented vessel



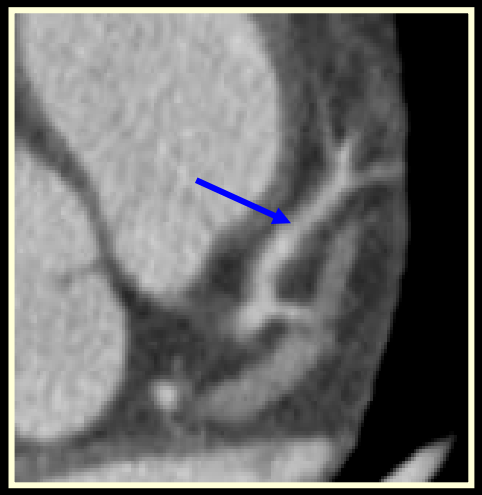
IVUS / OCT
stent visibility

MRI

MRI/MSCT

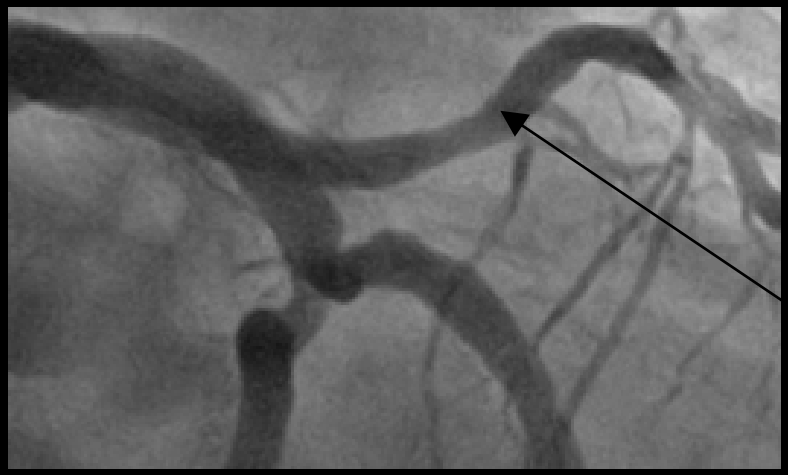
- No stent artefact
- Optimal vessel lumen imaging

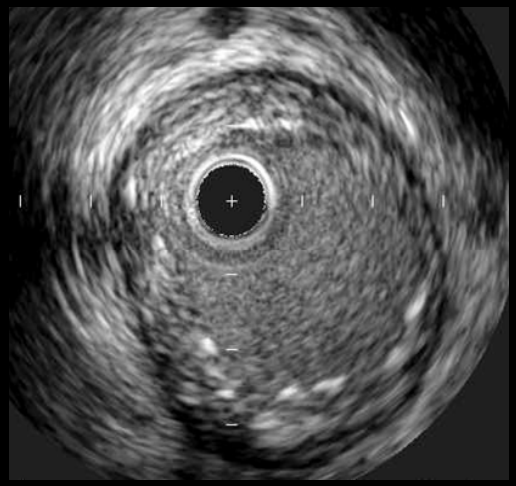
16 MSCT



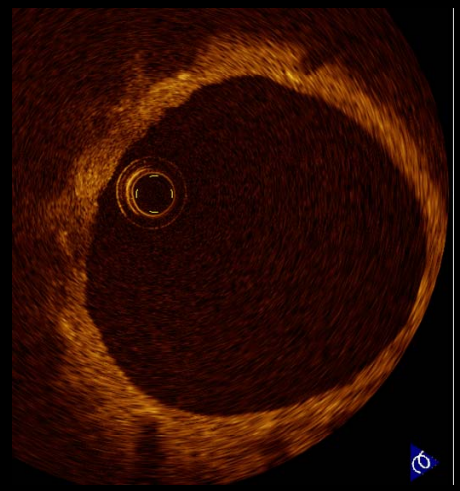
Source: Erbel et al, Herz 32 · 2007 · Nr. 4

Previous bare AMS devices demonstrated safety, but…





IVUS

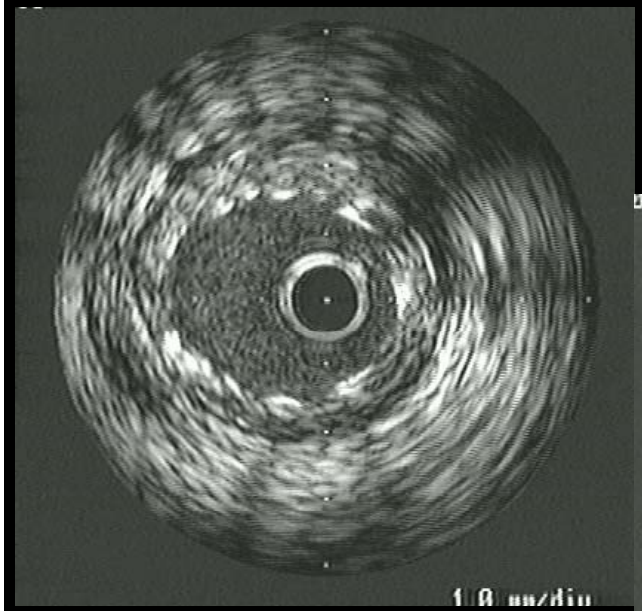


OCT

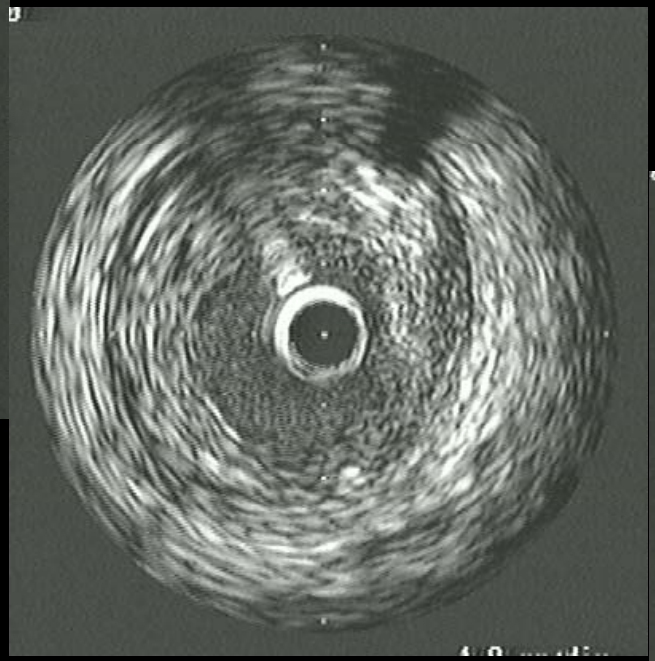
- Perfect ingrowth of AMS
- Safe in human coronary and peripheral arteries (150 patients)
  - No death, no MI, no scaffold thrombosis, no distal embolization, no excessive inflammation
  - Device success rate of 99.4%
- Absorbed as intended in several months
- Fully CT/MRI compatible

Source: Courtesy Dr Di Mario: PROGRESS AMS-1, long term results (15 months) showed perfect ingrowth

AUS 004-001



Post Implantation

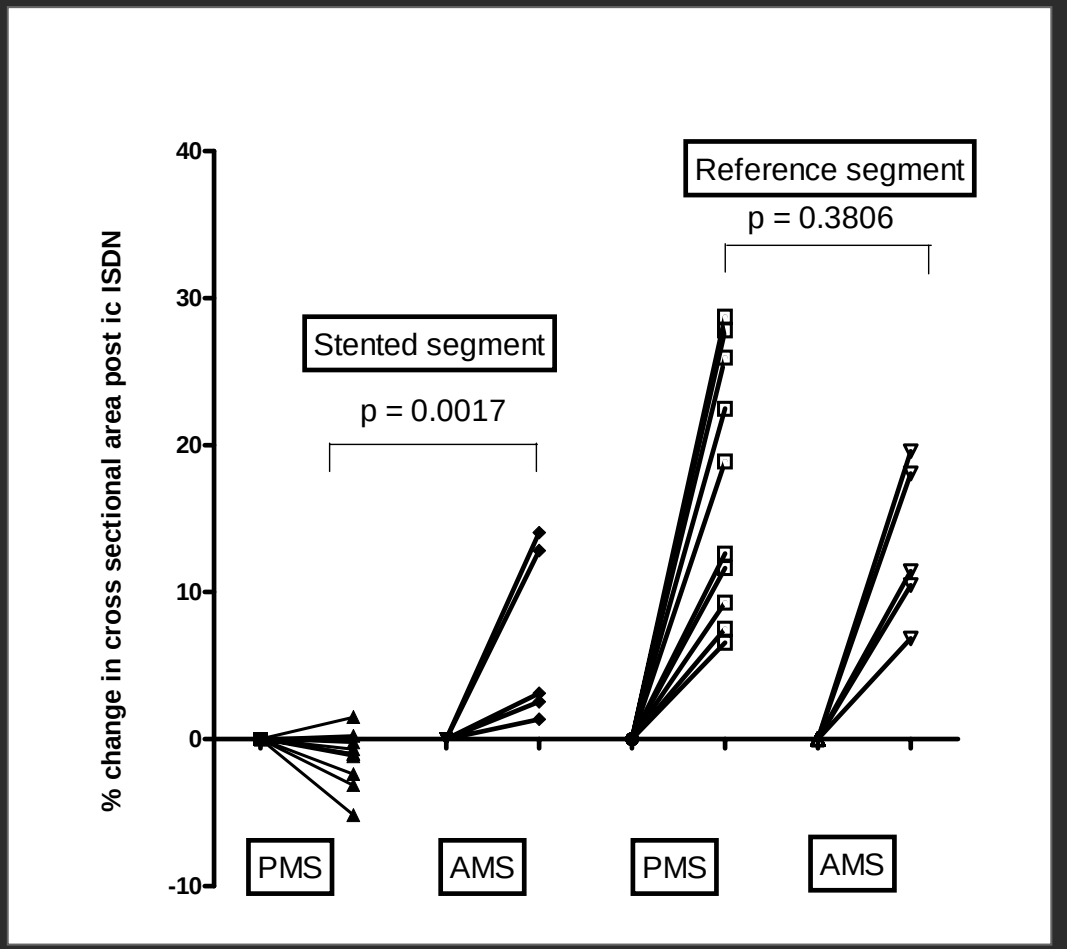


4 Months

16 Months

Vessel Reactivity

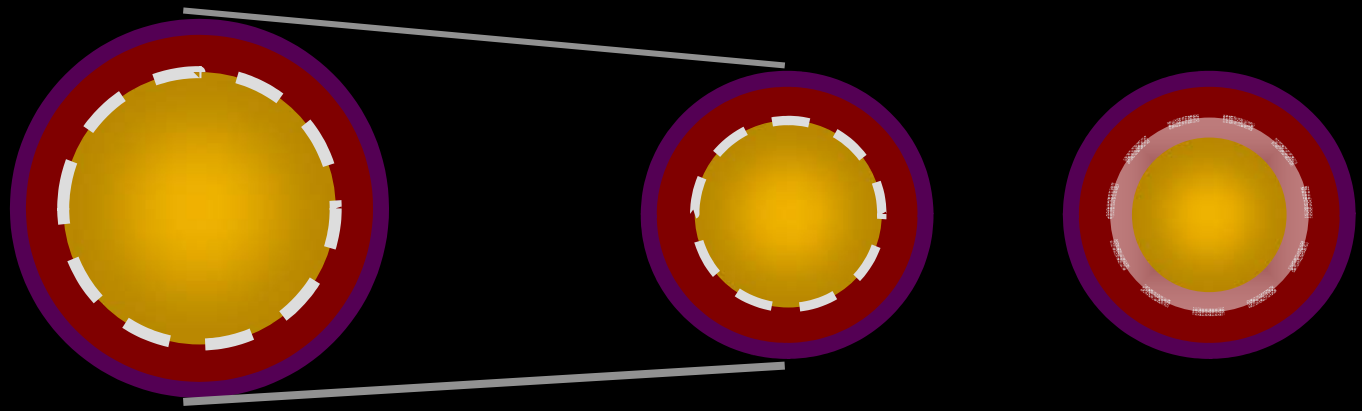
Intracoronary ISDN induced vasodilatation in Permanent Metal Stent (PMS) control patients and Absorbable Metal Stent (AMS) patients within stent and in proximal reference segments at 4 months post implant.



Courtesy of Dr Miles Dalby
Royal Brompton & Harefield

… failed to show sufficient efficacy

Two main drivers for restenosis



Contribution to lumen loss

Loss of stent scaffolding

53%

In-stent neointima

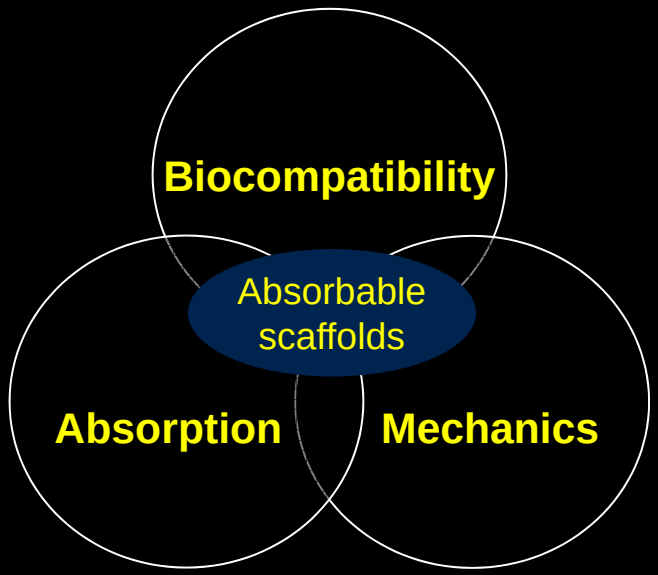
47%

Prolongation of stent scaffolding should reduce restenosis rate (ischemic driven TLR of 23.8% for AMS-1)

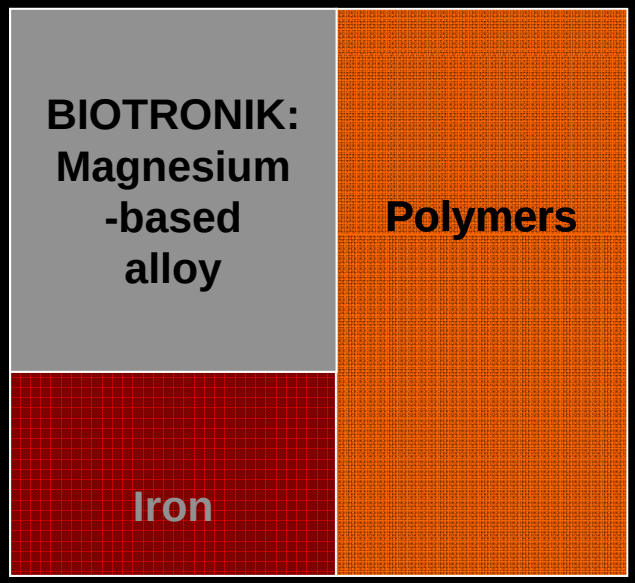
Source: PROGRESS AMS-1 IVUS

DREAMS is based on a proprietary magnesium technology

Requirements

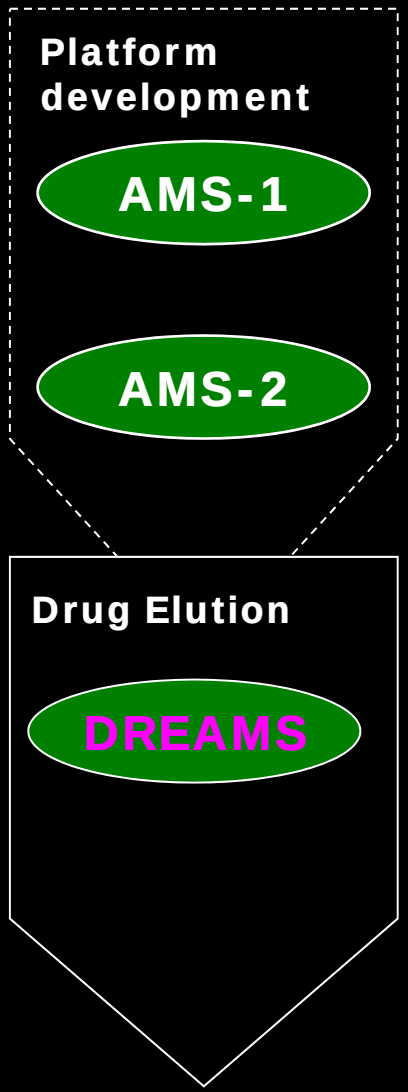


Absorbable materials



For coronary scaffolds, tailor-made magnesium alloys provide the best balance between biocompatibility, mechanical properties and absorption characteristics

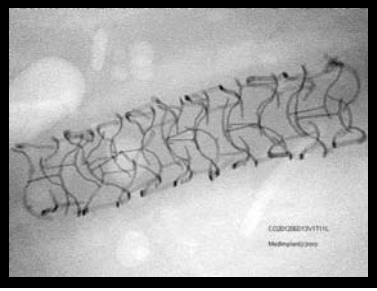
DREAMS evolves as a new therapy concept and addresses the two main limitations of bare magnesium scaffolds

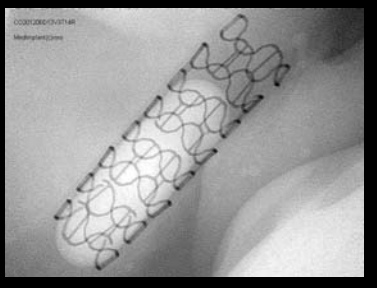


First generation device
- 4-crown design

Enhanced platform with prolonged stability
- Refined alloy providing 2-3 times slower degradation
- Approximately 30% thinner struts

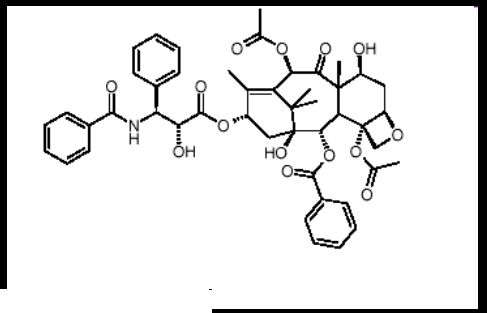
Drug eluting system for vascular restoration
- AMS-2 platform
- Degradable polymer
- Paclitaxel elution

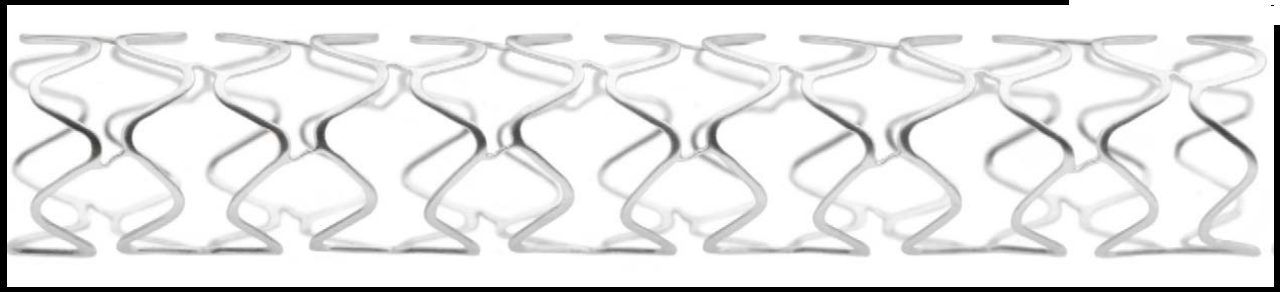




Why Paclitaxel...

- More than 5 million Paclitaxel eluting stents implanted
- More than 15 clinical trials with Paclitaxel eluting stents demonstrating safety & efficacy
- The only drug working in DEB and showing convincing results
- Very stable in combination with magnesium
- Allows safe degradation and inhibition of NIH



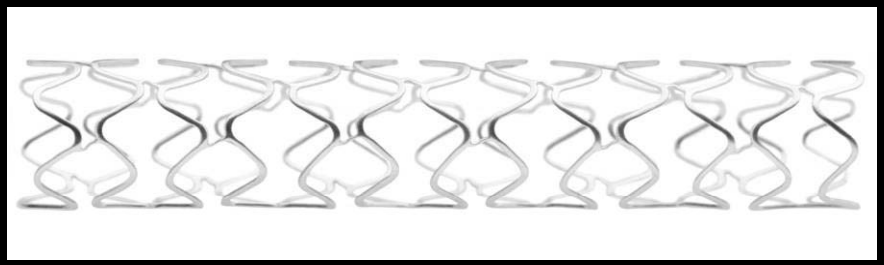


DREAMS, the DRug Eluting Absorbable Metal Scaffold is fully degradable

Drug carrier
- Fast degrading polymer

Backbone
- Customized Mg-alloy
- Good biocompatibility

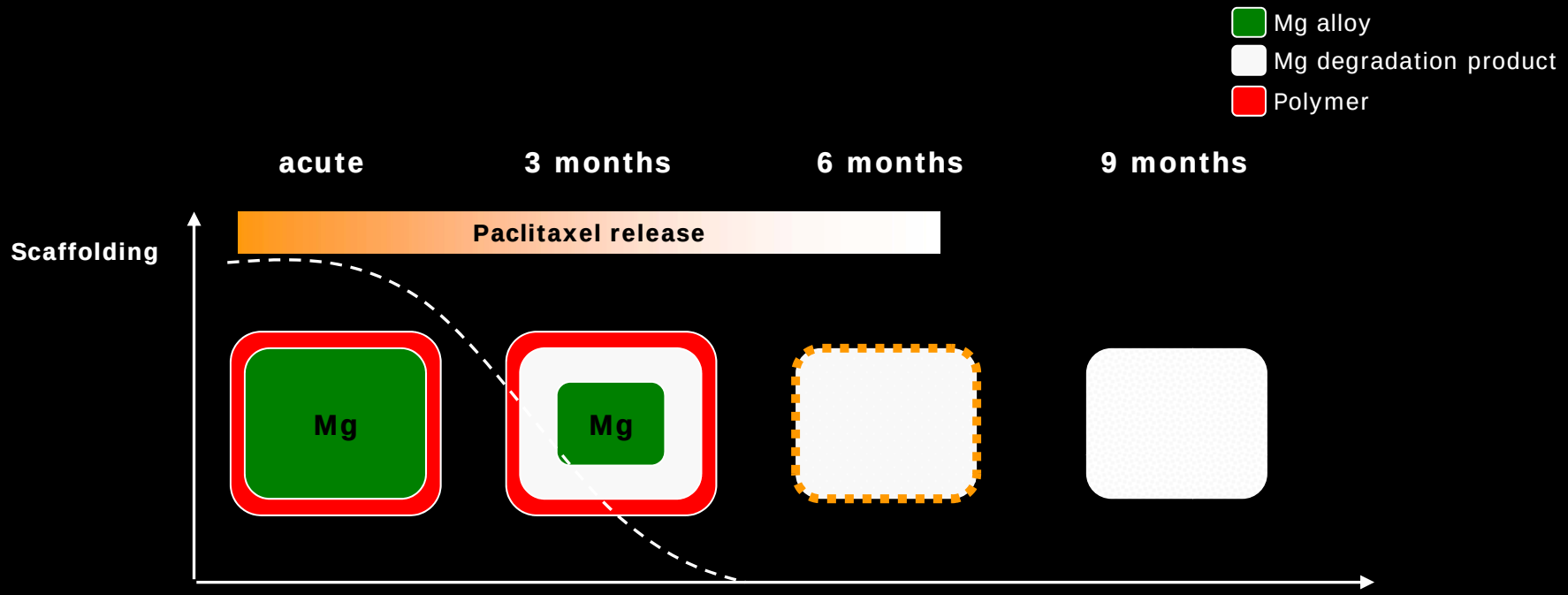
Drug
- Antiproliferative paclitaxel



Delivery system
- Modified PRO-Kinetic

Sizes used in FIM
- 3.25/3.5 x 16
- 6F compatibility

DREAMS provides scaffolding and paclitaxel release up to 3 months



- Mg degradation (conversion)
- Stable drug carrier layer
- Diffusion controlled drug release

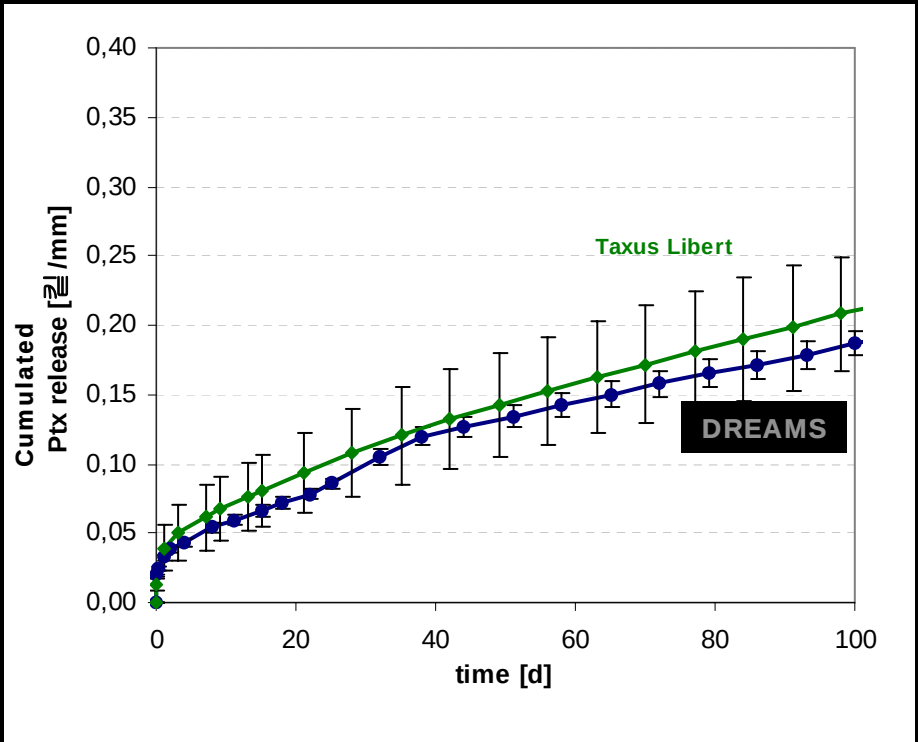
- Mg degradation completed
- Drug release completed
- Degradation of polymer

- Drug carrier layer degradation completed
- Beginning disintegration of Mg degradation product

Source: preclinical studies, data on file

First generation DREAMS shows in vitro elution behavior comparable with Taxus

DREAMS drug elution

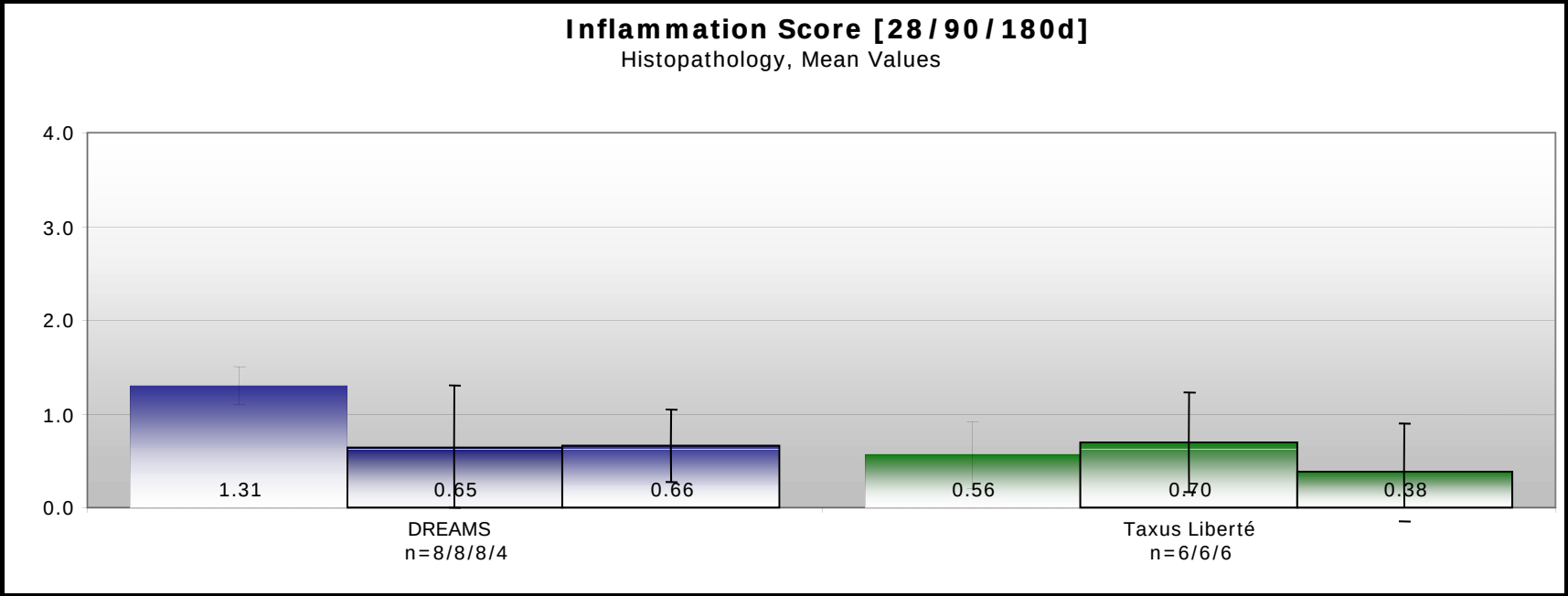


- High stability of paclitaxel allows to control processes in this system comprising a degradable backbone and a degradable drug carrier
- Based on preclinical tests, elution time in-vivo elution is estimated at 3 months

Source: in vitro measurements, data on file

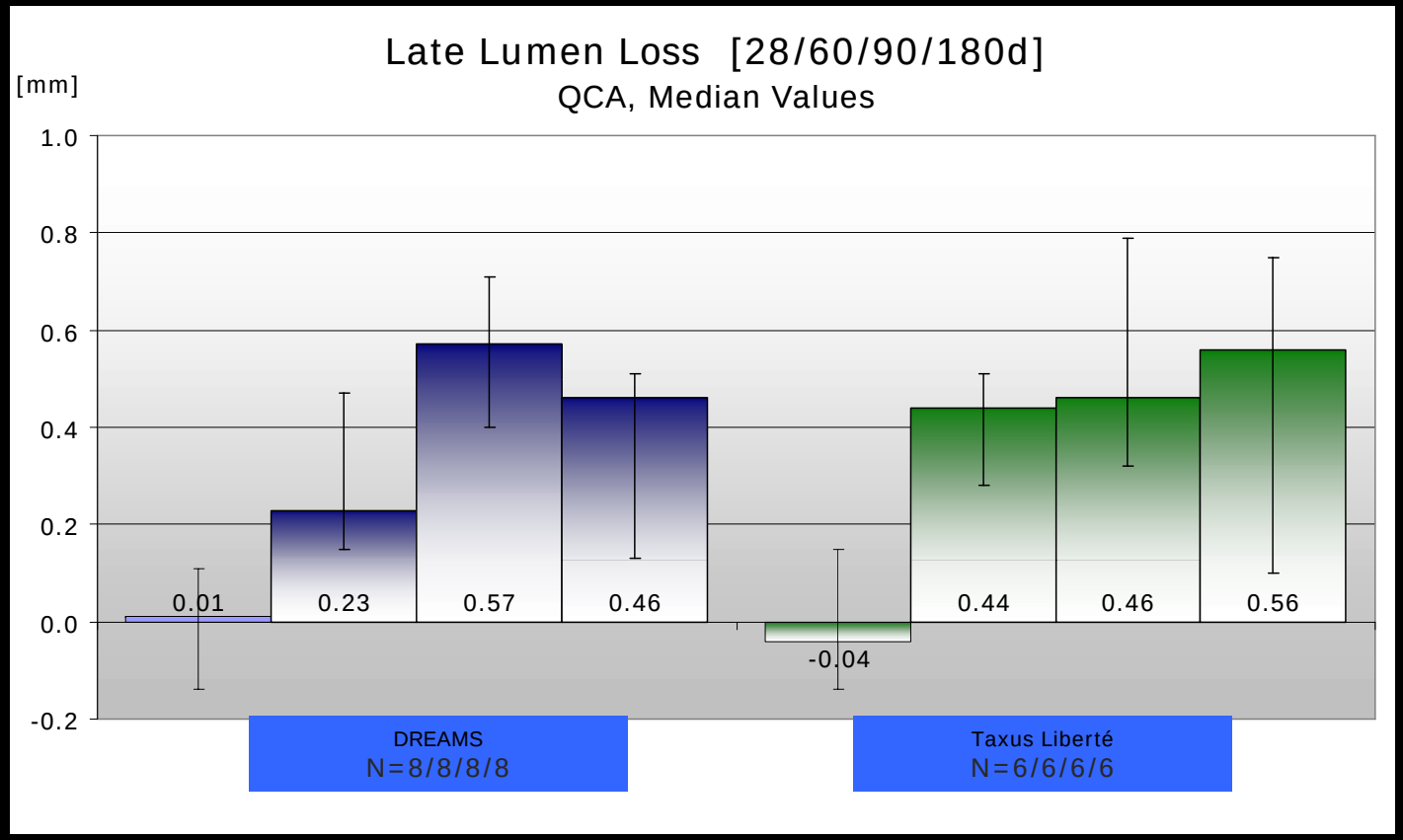
DREAMS shows low inflammation scores - comparable to Taxus

- Comparison between DREAMS and Taxus Liberté control shows low inflammation scores at 28, 90 and 180 days
- Minor increase of inflammation at 28 days seen in the DREAMS arm due to degradation of base materials



Source: AccelLAB preclinical studies, data on file

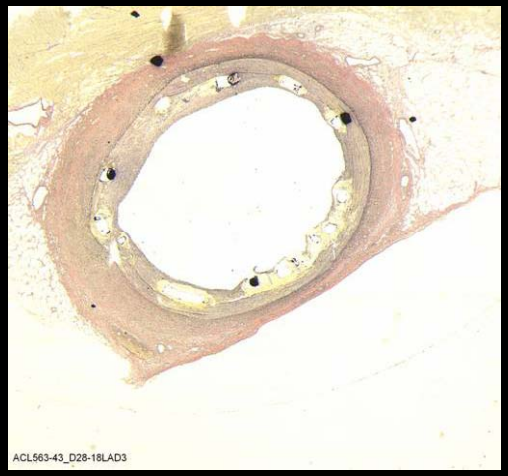
DREAMS late lumen loss is comparable to Taxus

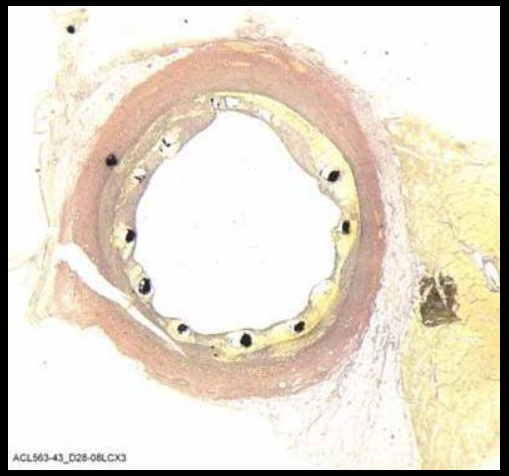


Source: AccelLAB preclinical studies, data on file

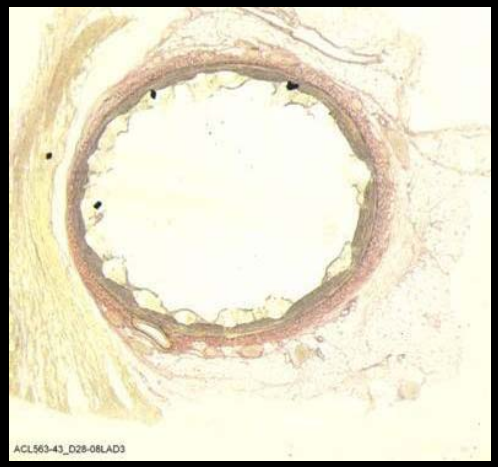
Histological Images at 28 days show fast healing of DREAMS

DREAMS





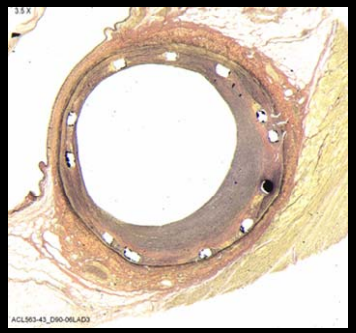
Reference (Taxus)



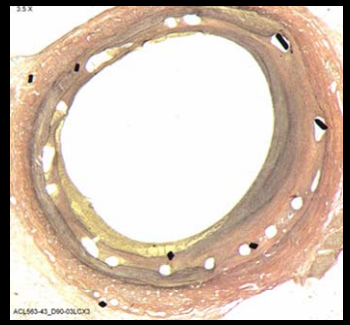
Source: AccelLAB preclinical studies, data on file
All photos same magnitude and scale

Histological Images at 90 days show nearly complete healing in DREAMS group

DREAMS*



Reference (Taxus)

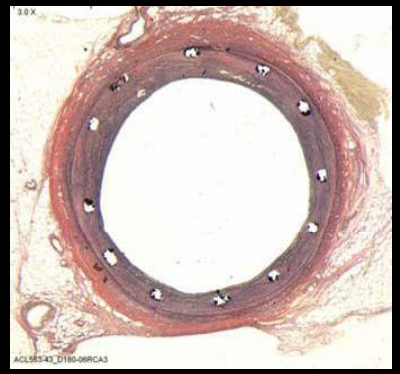


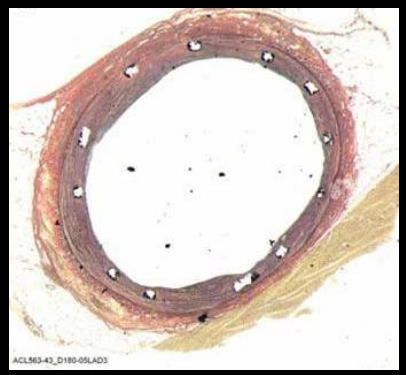
*DREAMS vessels are smaller than actual due to shrinkage during tissue processing (no scaffolding as in reference group)

Source: AccelLAB preclinical studies, data on file
All photos same magnitude and scale

At 180 days there is no catch-up after complete drug release of DREAMS

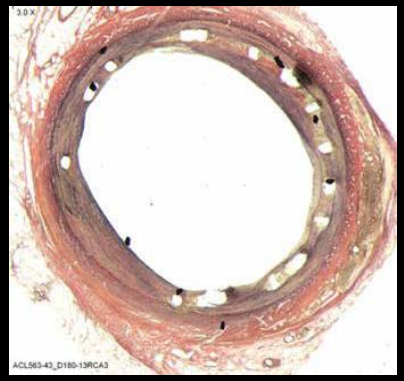
DREAMS





Black spots above represent Mg degradation product (amorphous Calcium phosphate phase)

Reference (Taxus)



Source: AccelLAB preclinical studies, data on file
All photos same magnitude and scale

BIOSOLVE-I: 47 patients enrolled in 6 centers
Angiography Follow-up will be completed in 2011

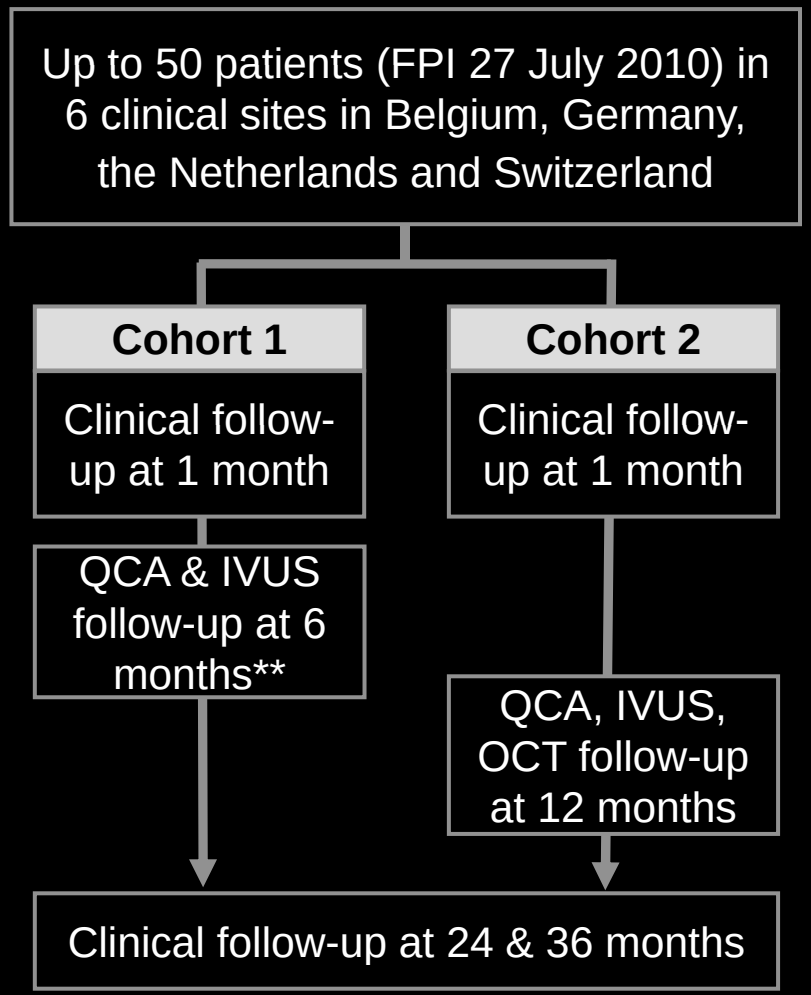
Study Design

DESIGN: Prospective, multi-centre, first in man trial

PRINCIPAL INVESTIGATOR:
J. Koolen, Eindhoven, The Netherlands

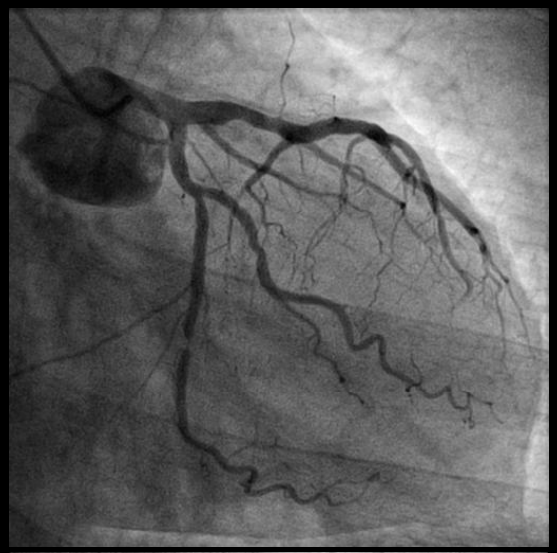
PRIMARY ENDPOINT: TLF* at 6 months (cohort 1) and 12 months (cohort 2)

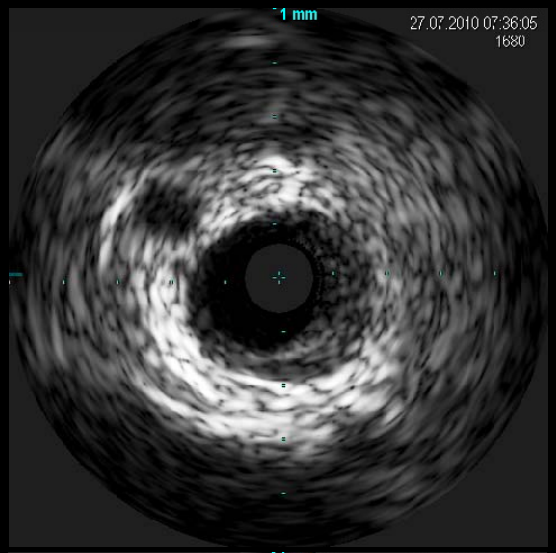
PARTICIPATION CENTERS:
Belgium: S. Verheye, Antwerpen
Germany: R. Erbel, Essen,
M. Haude, Neuss,
C. Hehrlein, Freiburg
Switzerland: P. Erne, Luzern

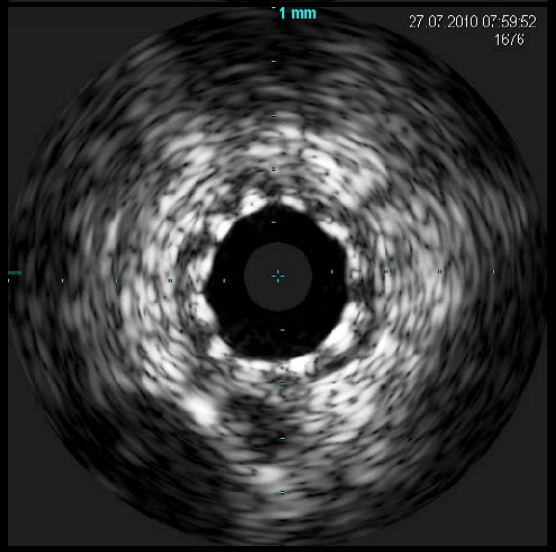


* Composite of cardiac death, myocardial infarction and clinically driven TLR. ** optional vasomotion testing

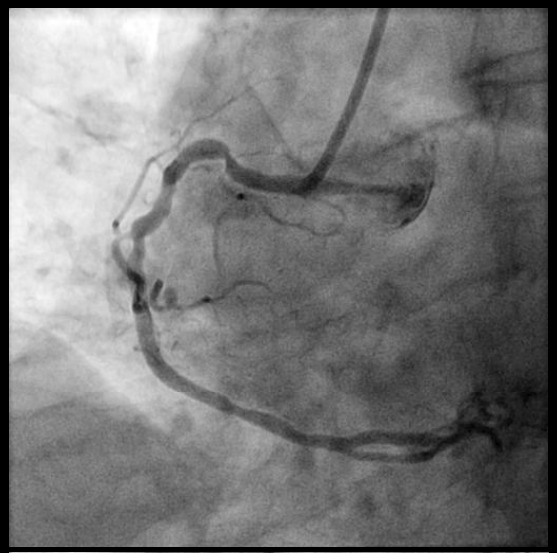
Case 01
COURTESY OF Dr Haude Biosolve 1 PI

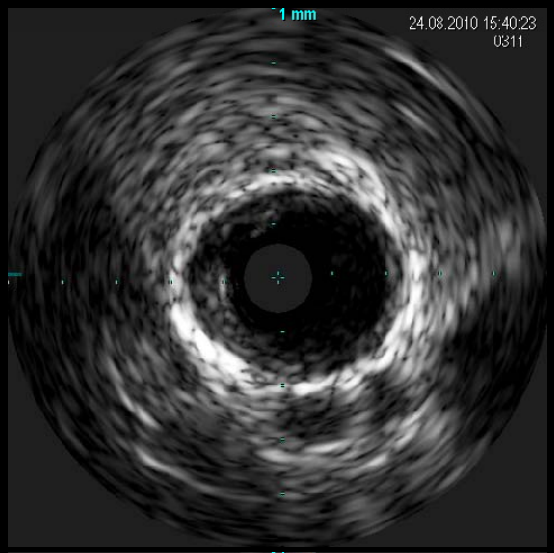


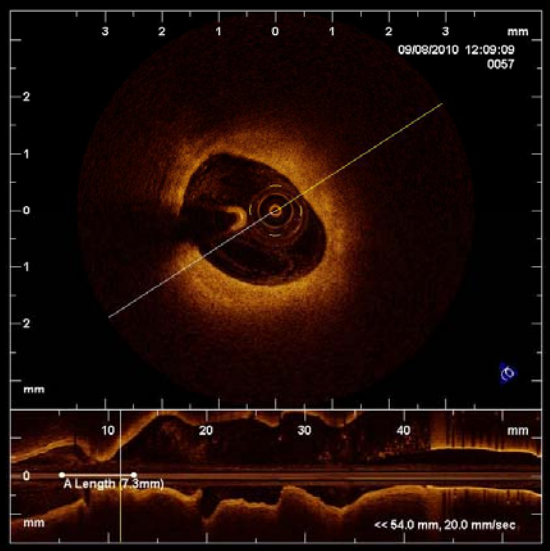




Case 02




1 mm
24.08.2010 15:40:23
0311


3 2 1 0 1 2 3 mm
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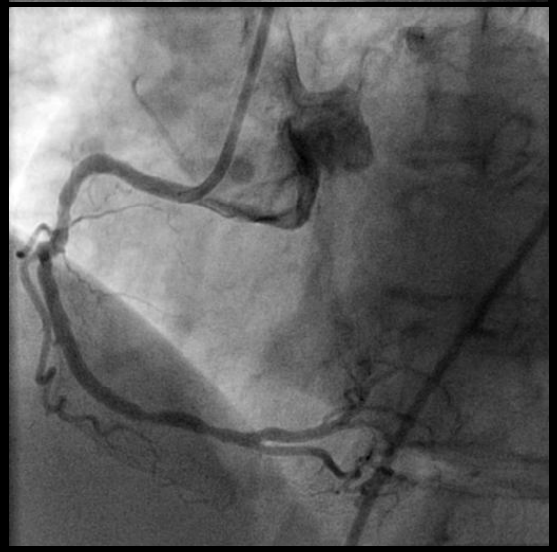
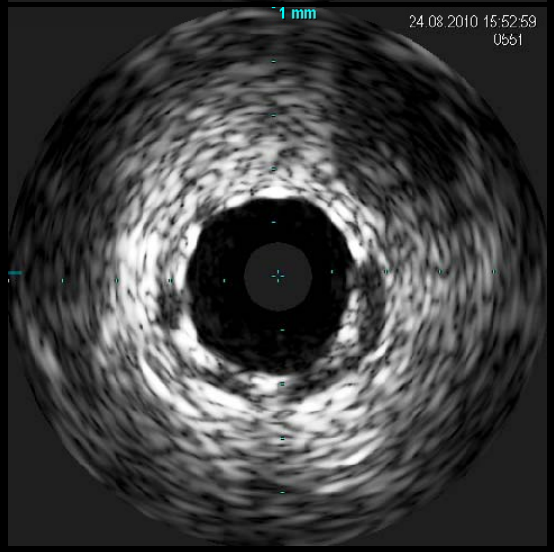
0057
2
1
0
1
2
mm
10 20 30 40 mm
0
A Length (7.3mm)
mm
<< 54.0 mm, 20.0 mm/sec




1 mm
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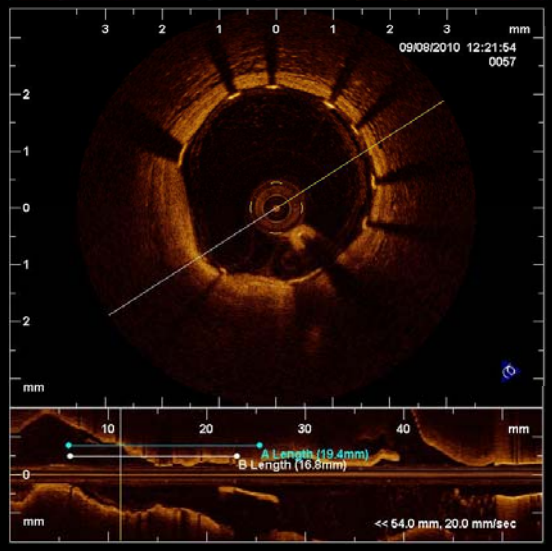
0551


3 2 1 0 1 2 3 mm
09/09/2010 12:21:54
0057
2
1
0
1
2
mm
10 20 30 40 mm
A Length (19.4mm)
B Length (16.8mm)
0
mm
<< 54.0 mm, 20.0 mm/sec

Conclusions

- The development of metallic bioabsorbable scaffolding is challenging
- The stents struts are thicker when compared to metallic durable stents
- Radial force issues could lead to immediate and early recoil
- Drug elution is mandatory to inhibit neointima proliferation
- Harmonization of the degradation of the alloy the biodegradable carrier and the drug are essential for a successful program