Can BVS Replace the Metal Stent?

Recent Academic

Current Status and Future Perspective

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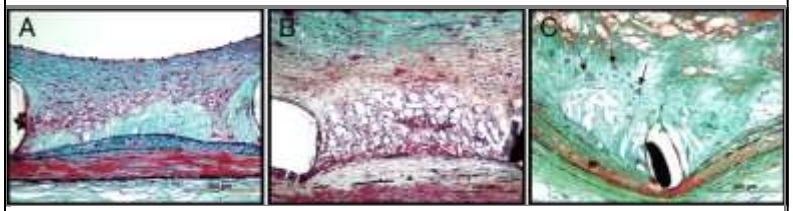
Limitations and Unmet Needs of Metal Stents

Neoatherosclerosis

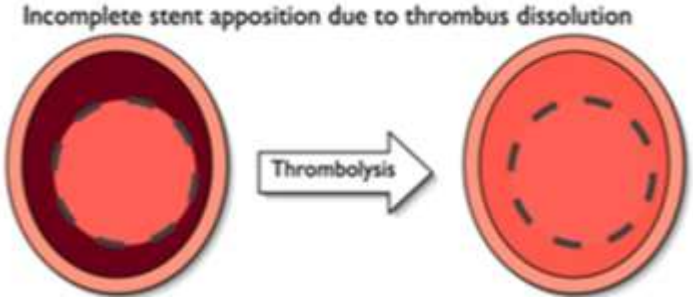
Nakazawa G et al. *JACC* 2011



Late Stent Thrombosis?
Late Restenosis ?

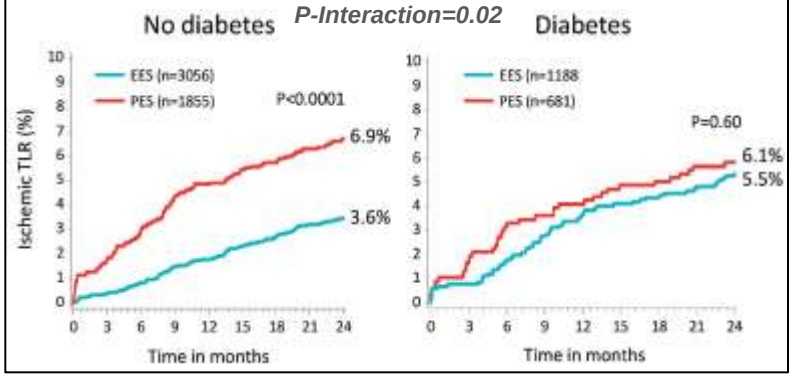
Acute MI

Cook S et al. *Circulation* 2009



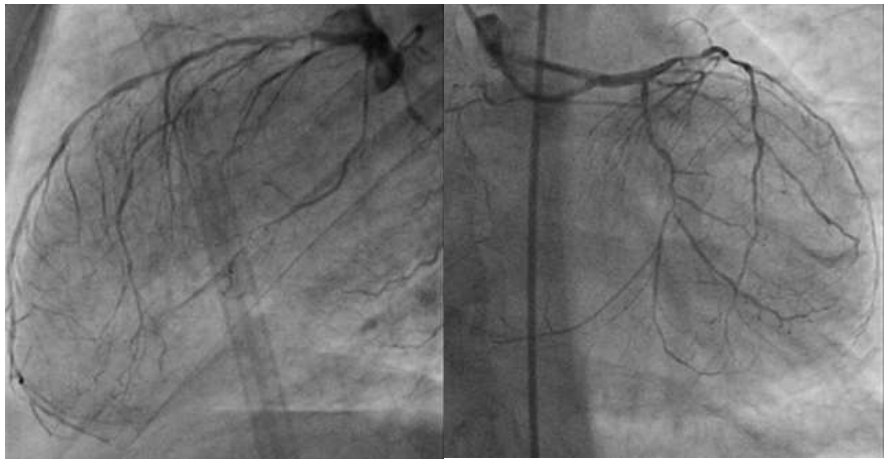
Diabetes

Stone GW et al. *Circulation* 2011



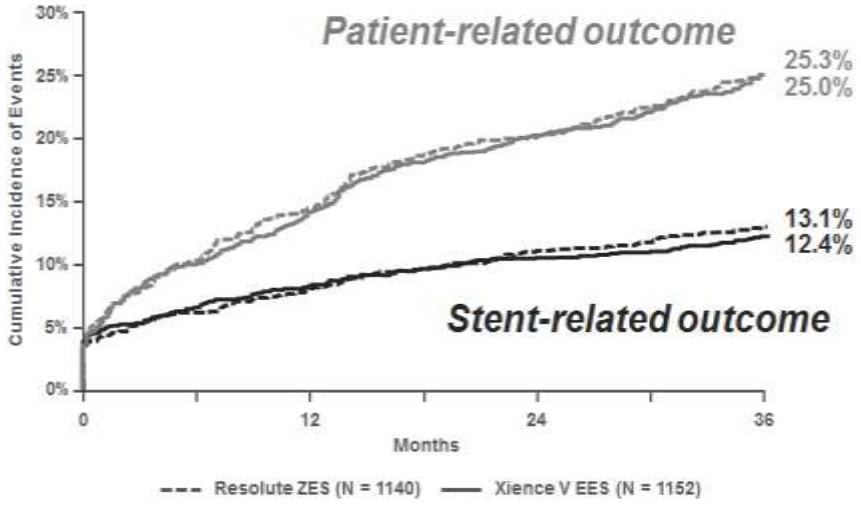
Diffused Multivessel CAD

Jolicoeur E et al. *CJC* 2012



CAD Progression

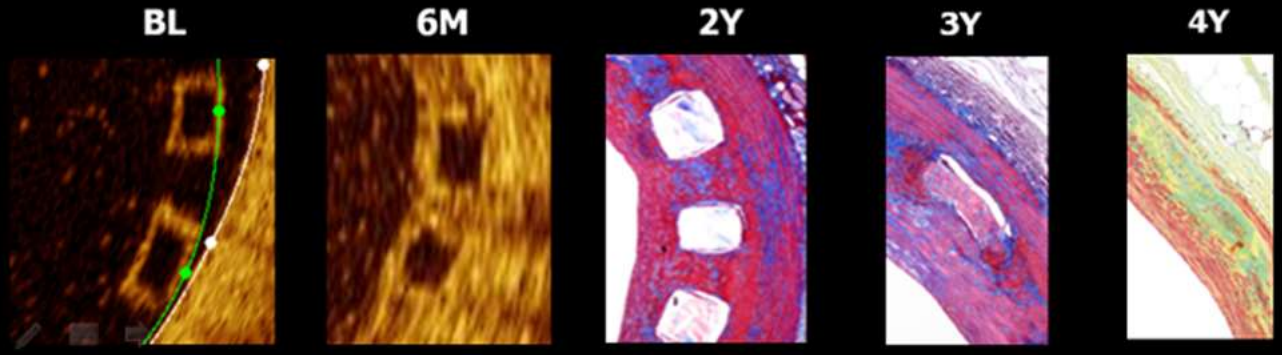
Silber S et al. *Lancet* 2011



BVS - Device Resorption; "They do their job and disappear"

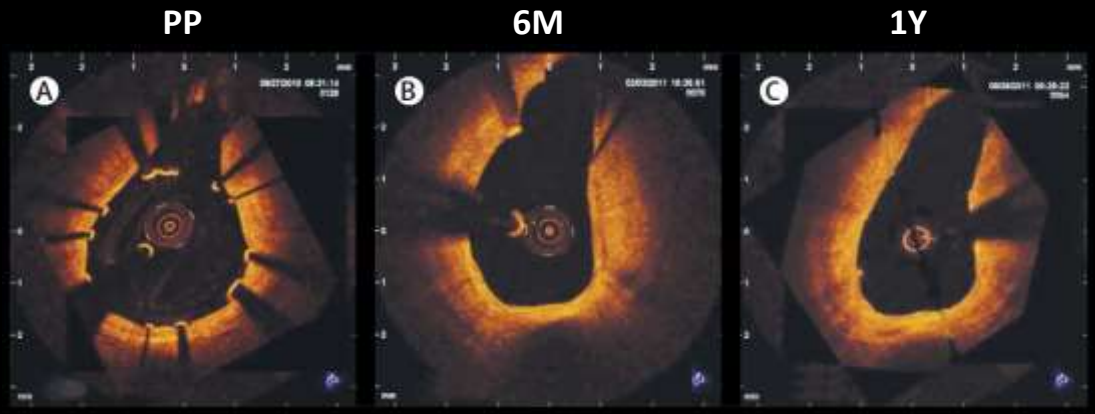
ABSORB BVS

Ormiston J et al. *Circ Cardiovasc Interv* 2012;5:620-32



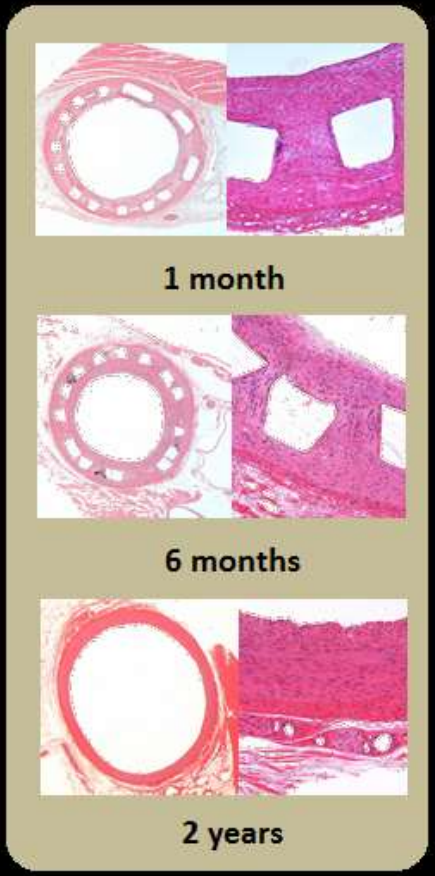
DREAMS

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



DESolve

Preclinical Studies



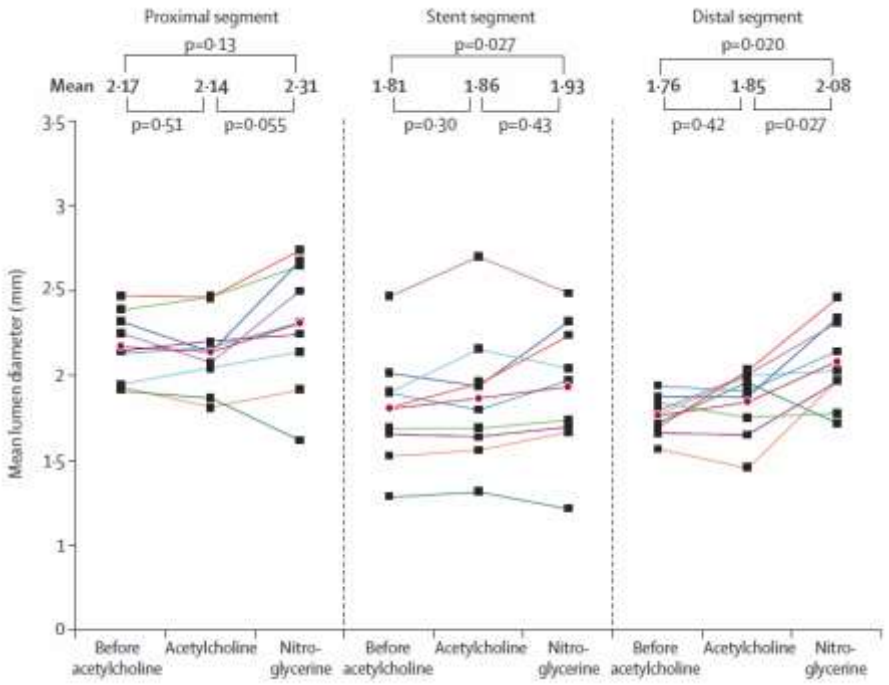
Potential Benefits of BVS

Potentials of Fully Bioresorbable Coronary Scaffolds

Serruys P et al. *Lancet* 2009;373:897-910

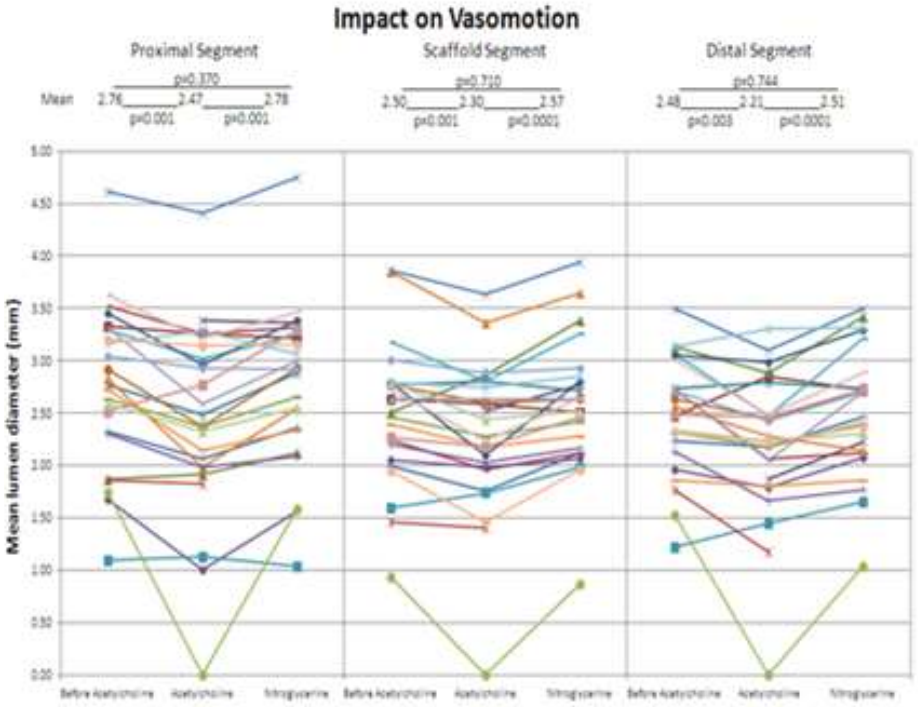
Vasomotion Restoration

ABSORB @ 2 years



Serruys P et al. *Lancet* 2009;373:897-910

BIOSOLVE-I

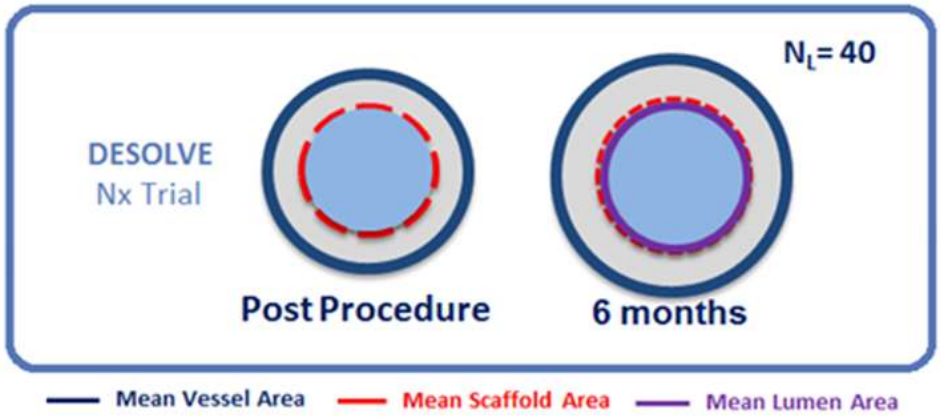


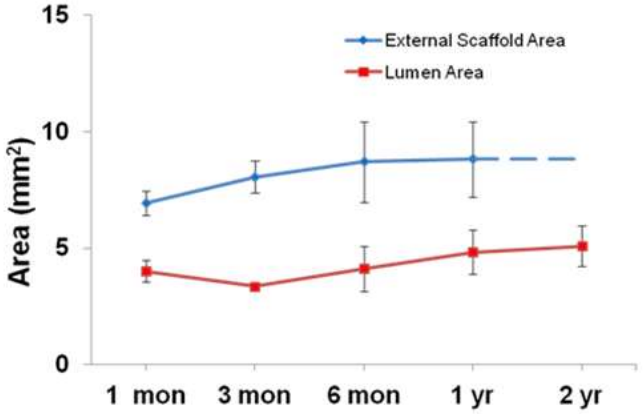
Haude M et al *Lancet* 2013; 381:836-44

Potentials of Fully Bioresorbable Coronary Scaffolds

Ormiston J et al. *Circ Cardiovasc Interv* 2012;5:620-32

Late Lumen Enlargement



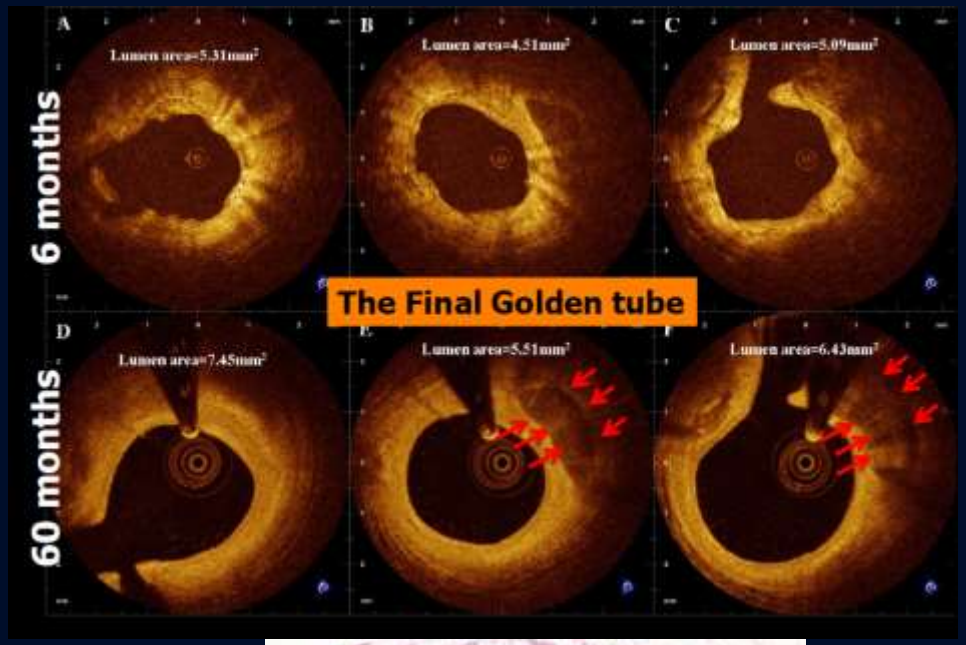


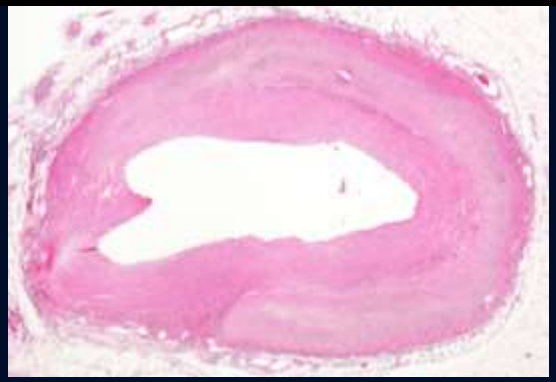
Potentials of Fully Bioresorbable Coronary Scaffolds

Brugaletta S et al. *Atherosclerosis* 2013

Neocap - Plaque Sealing

	BL	6 Ms (B1)	12 Ms (B2)	24 Ms (B1)	36 Ms (B2)
Neointimal Thick, μm	0	210	220	254	285
BVS area, mm^2	7.47 (B1) 7.73 (B2)	7.70	7.51	8.24	8.64
MLA, mm^2	7.23 (B1) 7.69 (B2)	6.07	6.01	5.99	6.09





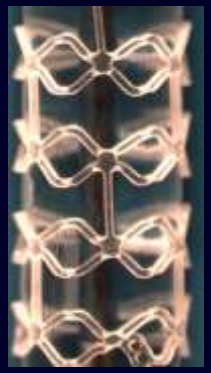
Potential Clinical Benefits of a Bioabsorbable DES…

- Provides *transient* vessel scaffolding when needed, "leaving nothing behind"
- Local drug release inhibits restenosis
- Restores vessel to natural state with normal function and healing responses
- Reduces need for long term DAPT
- Eliminates source of inflammation/ irritation
- Reduces late events (esp. SAT)
- Vessel free for future interventions; CABG

Current Technology of BVS

Bioresorbable Coronary Scaffolds




Van der Giessen *Circulation*

Tamai *Circulation*

Erbel *Lancet*

Ormiston *Lancet*

Jabara *PCR 2009*

Abizaid *PCR 2011*

Haude *Lancet*

1996 **2000** **2007** **2008** **2010** **2013**

Animal studies
polymeric scaffolds revealing excessive inflammatory reactions

Igaki Tamai
First fully biodegradable non drug eluting scaffold
N=15

AMS-1
first bioabsorbable metallic non drug-eluting scaffold
N=64

Bioresorbable vascular scaffold
first bioabsorbable drug eluting scaffold
N=31

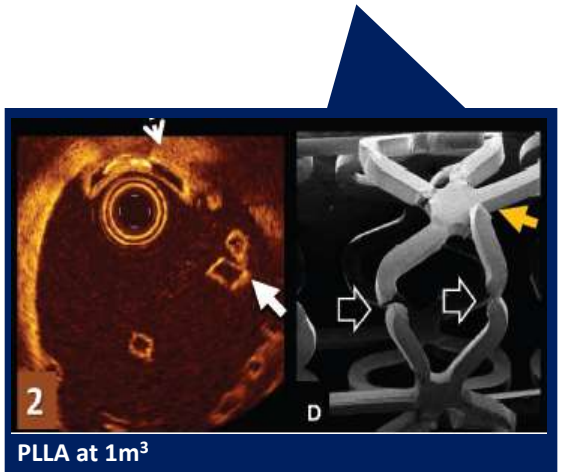
IDEAL BDS
Polyanhidride ester and salicylic acid, drug-eluting scaffold
N=11

REVA
Polycarbonate stent, radiopaque, non drug-eluting scaffold
N=31

DREAMS
first drug-eluting bioabsorbable metallic scaffold
N=22

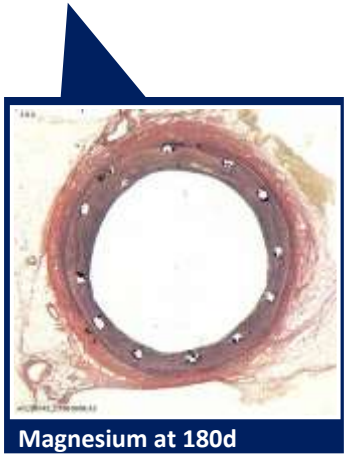
Key characteristics of absorbable scaffold materials

	Polymeric		Metallic
Material	**PLLA[1]**	**Iron[2]**	**Magnesium Alloy[2]**
Tensile Strength (MPa)	~30-45	300	280
Elongation (%)	2 – 6	25	23
Total Degradation Time	2-3 Years	> 4 years	9-12 months



PLLA at 1m[3]

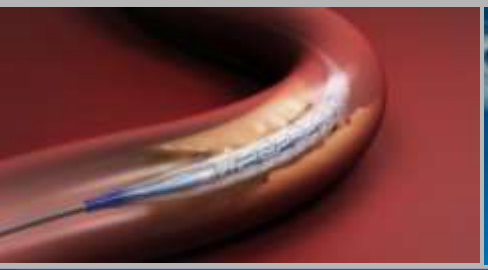
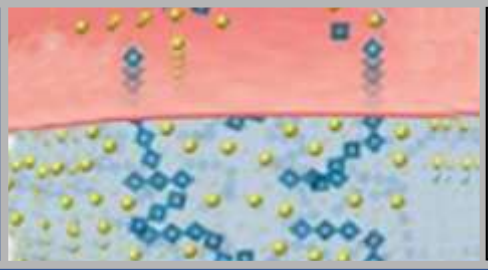

Iron at 28d


Magnesium at 180d

[1] Ratner DB, et al. Biomaterials Science: Introduction to Materials in Medicine, 2nd Edition. Elsevier Academic Press, 2004. [2] Hermanwan H, et al. Acta Biometerialia. 6 (2012):1693-1697. [3] Ormiston J et al. Circ Cardiovasc Interv 2011;4;535-538, Oct. 2011.

Clinical Data of Bioabsorbable Stent

Abbott Vascular Everolimus-Eluting Bioresorbable Vascular Scaffold

ML VISION Delivery System	Bioresorbable Device Platform	Bioresorbable Coating	Everolimus
• Seven generations of MULTI-LINK success • World-class deliverability	• Polylactide (PLLA) • Naturally resorbed, fully metabolized	• Polylactide (PDLLA) coating • Fully biodegradable	• Similar dose and release rate to XIENCE V
			

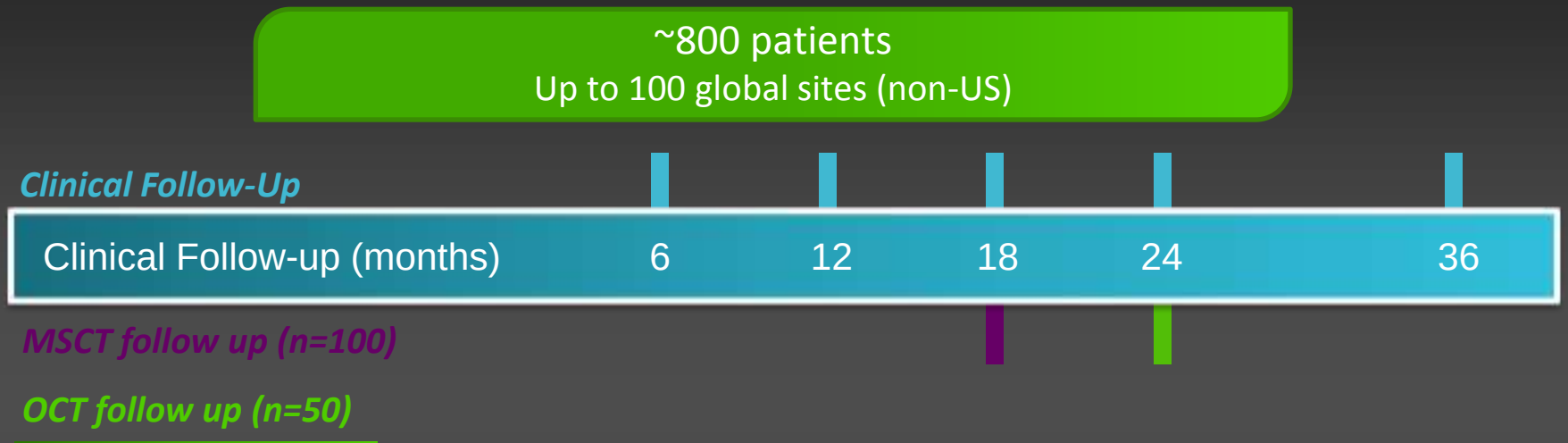
Investing in a Comprehensive ABSORB Clinical Trial Program

Total Patients Studied	**n=~599**	**n~930**	**n~5,674**	**n~13,453**	**n~13,453**	**n~13,453**

Note: Sample sizes reflect Absorb patients only.
* n= 10,000 f/u at 6 months. 1.000 patients f/u at 1 -3 years, 1.000 patients at 2-4 years

ABSORB EXTEND

Investigador Principal : Alexandre Abizaid
Instituto Dante Pazzanese de Cardiologia



Study Objective	**Continued Access trial. FPI: Jan 11, 2011**
Endpoints	**Typical PCI clinical endpoints**
Treatment	**Up to 2 *de novo* lesions in different epicardial vessels** **Planned overlapping allowed in lesions >22 and ≤ 28 mm**
Device Sizes	**Scaffold diameters: 2.5, 3.0, 3.5 mm** **Scaffold lengths: 12*, 18, 28 mm**

ABSORB EXTEND

Non-Hierarchical	6 Months* n = 450	12 Months* n = 450
Cardiac Death % (n)	0.2 (1)**	0.2 (1)**
Myocardial Infarction % (n)	2.7 (12)	2.9 (13)
Q-wave MI	0.7 (3)	0.9 (4)
Non Q-wave MI	2.0 (9)	2.0 (9)
Ischemia Driven TLR % (n)	0.4 (2)	1.8 (8)
PCI	0.4 (2)	1.6 (7)
CABG	0.0 (0)	0.2 (1)
Hierarchical MACE % (n)	2.9 (13)	4.2 (19)
Scaffold Thrombosis (ARC Def/Prob) % (n)	0.7 (3)	0.9 (4)

Chevalier, EXTEND preliminary results, Rotterdam PCR Focus on BVS, 2013

ABSORB EXTEND Propensity Score Matched Clinical Outcomes: 2 Years

	Absorb (EXTEND, N = 178)	XIENCE V (SP123, N = 293)	P
NON-HIERARCHICAL COMPONENTS			
Cardiac Death %	0.0	1.4	0.30
Myocardial Infarction %	4.5	4.4	1.00
Ischemia Driven TLR %	3.4	3.8	1.00
MACE %	6.7	8.9	0.49
TVF %	7.3	12.3	0.09
TLF %	6.2	8.2	0.47
Scaffold Thrombosis (ARC Def/Prob) %	0.6	1.4	0.65

Pooled Analysis; BVS vs. EES at 1 Year

Non-Hierarchical	Absorb BVS (N = 558)	XIENCE V (N = 672)	P value
Cardiac Death %	0.3	0.6	0.35
Myocardial Infarction %	3.9	2.1	0.06
Ischemia Driven TLR %	1.6	3.2	0.08
Hierarchical MACE %	5.2	5.5	0.81
Hierarchical TVF %	5.5	8.6	0.04
Hierarchical TLF %	5.2	5.0	0.91
Scaffold Thrombosis (ARC Def/Prob) %	0.5	0.5	0.93

Absorb BVS Cohort: Pooled from ABSORB EXTEND and ABSORB Cohort B trials
XIENCE V Cohort: Pooled from XIENCE V arms of SPIRIT FIRST, II, and III trials.

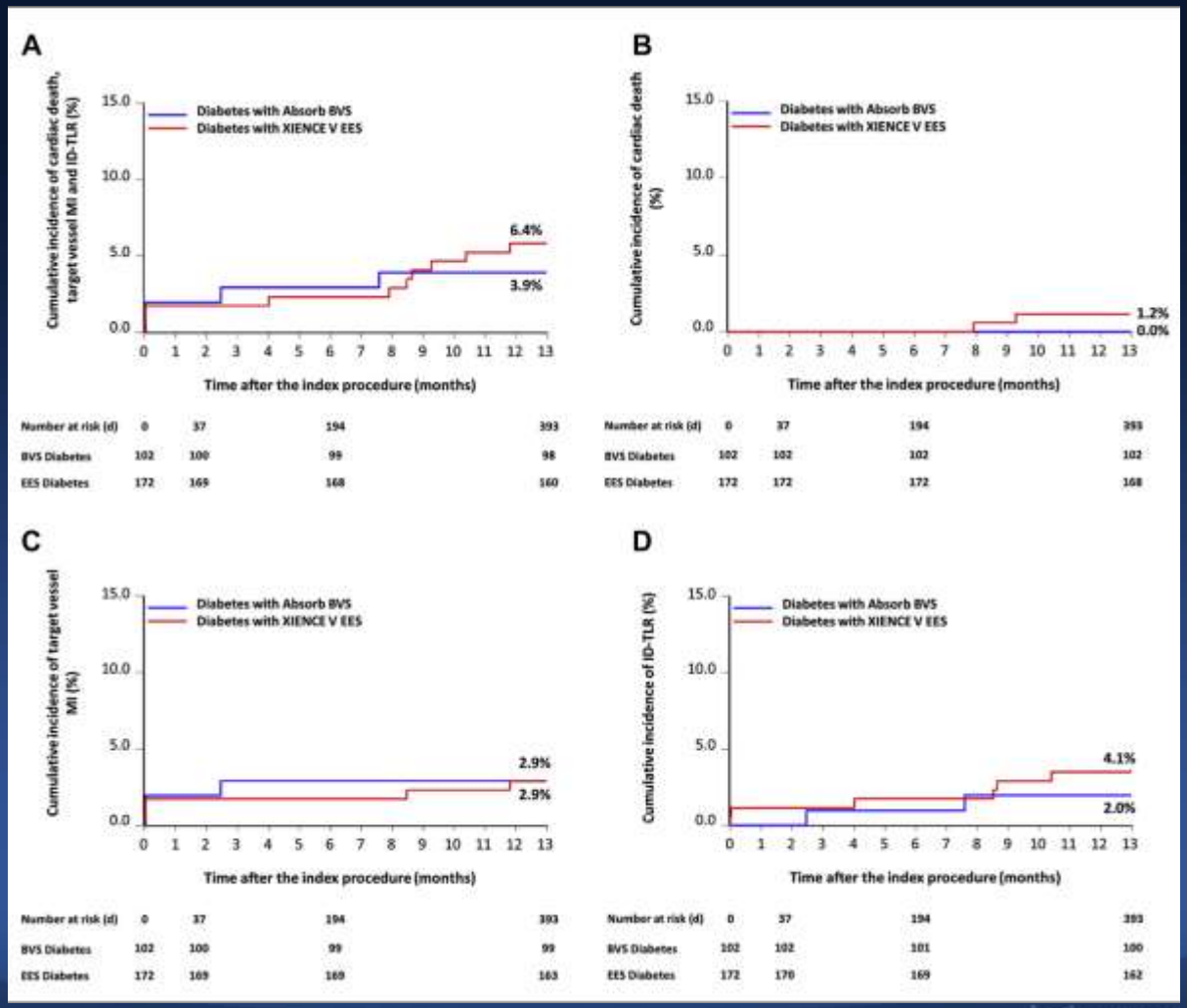
#Analysis adjusted for patient baseline demographics, risk factors and lesion characteristics with Inverse Propensity Scores Weighted method

Chevalier, R , ESC, 2013

Absorb vs. EES in DM Patients

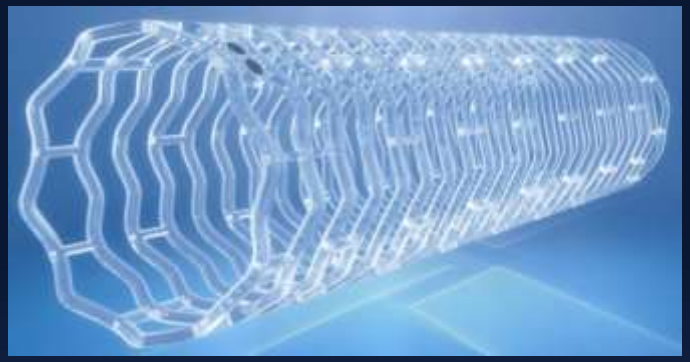
A Pooled Analysis of the ABSORB and the SPIRIT Trials

Propensity-Matched

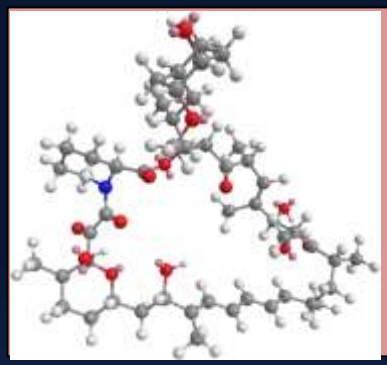


J Am Coll Cardiol Intv 2014;7:482–93

DESolve Nx Bioresorbable Scaffold

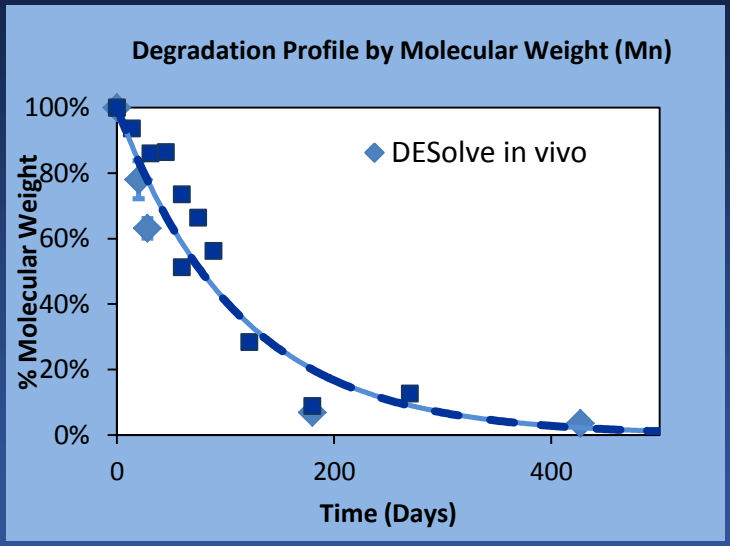


Novolimus-eluting PLLA-based polymer scaffold

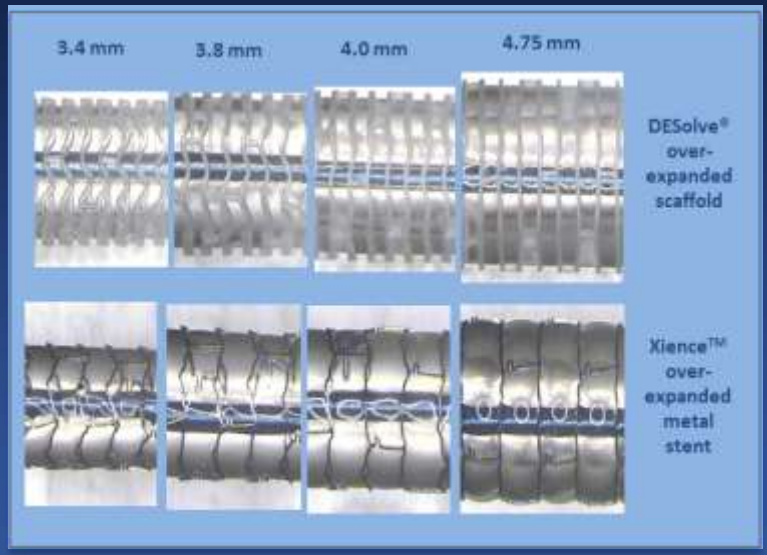


Formula:
$C_{50}H_{77}NO_{13}$
MW: 900

Novolimus – a metabolite of sirolimus

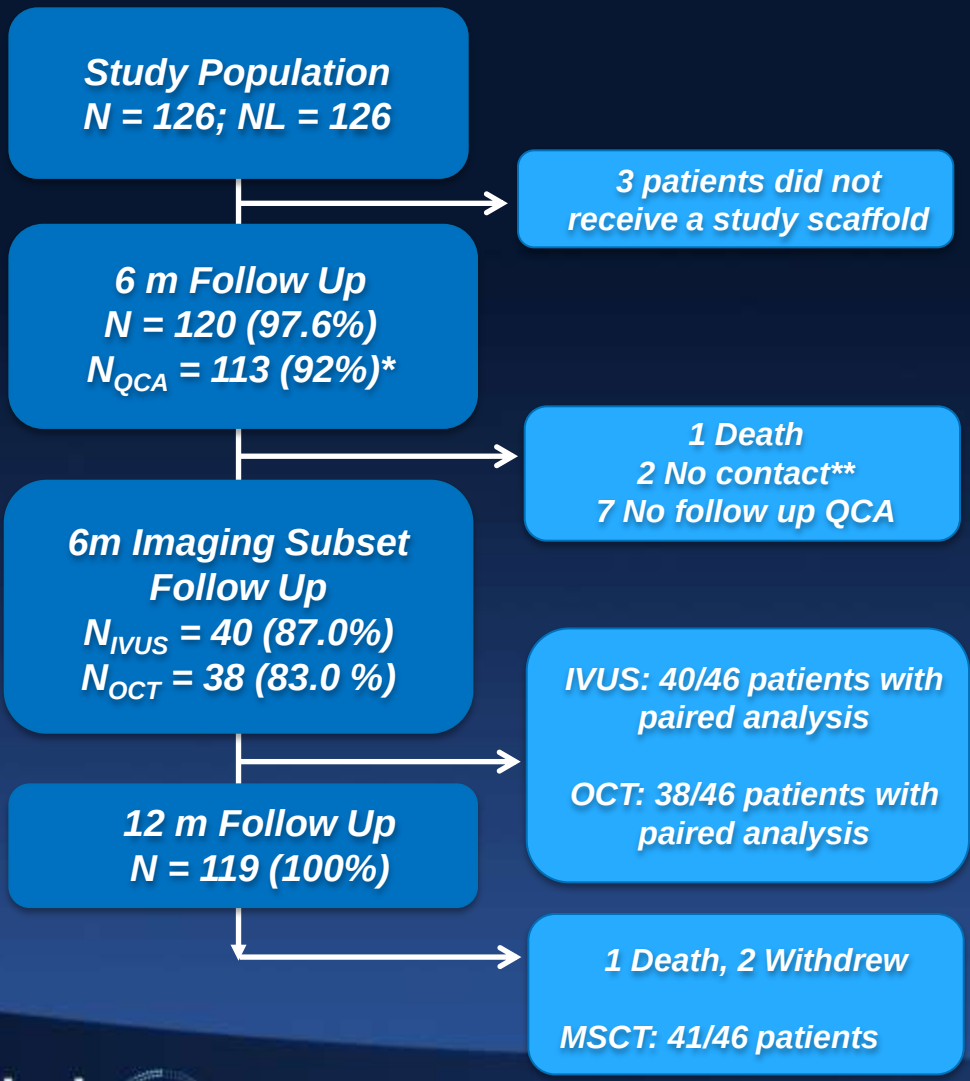


DESolve degrades in approximately 1 year



Favorable expansion range (safety from fracture)

DESolve Nx Trial (N=126)



Patient Characteristics, % unless stated	N = 126
Age, years (mean±SD)	62.0 ± 9.8
Male	68.3%
Diabetes mellitus	21.4%
Hypercholesterolemia	70.6%
Hypertension	70.6%
Previous MI	44.4%
Previous PCI	35.7%
Unstable Angina	12.7%
Lesion Characteristics (mean ± SD), or %	**N_L = 126**
Lesion Length, mm	11.2 ± 3.8
AHA/ACC Lesion class B2 / C	34.0%
Moderate / Heavy Calcification	18.3%

QCA Results at 6 Months

In-Scaffold Analysis	Baseline N_L= 126	Post procedure N_L= 126	6 months N_L= 113
RVD (mm)	3.06 ± 0.31	3.09 ± 0.26	3.01 ± 0.29
MLD (mm)	0.92 ± 0.40	2.67 ± 0.28	2.45 ± 0.44
Acute gain (mm)		1.73 ± 0.45	
Acute Recoil (%)		6.6%	
LLL at 6-months (mm)			0.21 ± 0.34
Median Late Loss (mm)			0.11 (0.04 , 0.21)
Diameter Stenosis (%)	69.9 ±12.3	13.5 ± 7.8	18.3 ± 13.6
In-Segment Binary Restenosis* n (%)			4 (3.5%)

Values are mean ± SD; % (n), or Median (interquartile range 25%, 75%)
MLD – Minimum luminal diameter; LLL – late lumen loss.
**** In-Segment: In-scaffold + 5mm proximal and distal to scaffold; 3 cases of geographic miss***

Clinical Outcomes at 12 Months

Hierarchical Events 0 to 180 days, n (%)	(N = 123)*
Major Adverse Cardiac Events	**5.69%**
Cardiac Death	2 (1.6%)
Target vessel MI	1 (0.8%)
Q-wave MI	0 (0.0%)
Non-Q- wave MI	1 (0.8%)
Clinically Indicated-TLR PCI	4 (3.3%)
Def/prob Stent Thrombosis+	1 (0.8%)

*Modified Intent to Treat = patients with scaffold implanted
+ ARC-defined

Safety and performance of the drug-eluting absorbable metal scaffold (DREAMS) in patients with de-novo coronary lesions: 12 month results of the prospective, multicentre, first-in-man BIOSOLVE-I trial

Michael Haude, Raimund Erbel, Paul Erne, Stefan Verheye, Hubertus Degen, Dirk Böse, Paul Vermeersch, Inge Wijnbergen, Neil Weissman, Francesco Prati, Ron Waksman, Jacques Koolen

Lancet 2013; 381: 836–44

Published Online January 15, 2013 http://dx.doi.org/10.1016/S0140-6736(12)61765-6

See Comment page 787

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Summary

Background Bioabsorbable vascular scaffolds were developed to overcome limitations of permanent bare-metal or drug-eluting coronary stents—ie, stent thrombosis (despite prolonged dual antiplatelet therapy), the life-long presence of a caged vessel segment that does not allow vasomotion or remodelling, and chronic vessel wall inflammation. We assessed the safety and performance of a new magnesium-based paclitaxel-eluting absorbable metal scaffold in symptomatic patients with de-novo coronary lesions.

Methods We did a prospective, multicentre, first-in-man trial (BIOSOLVE-1) of the drug-eluting absorbable metal scaffold (DREAMS). 46 patients with 47 lesions were enrolled at five European centres. The primary endpoint was target lesion failure, a composite of cardiac death, target vessel myocardial infarction, and clinically driven target lesion revascularisation, at 6 and 12 months. Clinical follow-up was scheduled at 1, 6, 12, 24, and 36 months. Patients were consecutively assigned to angiographic and intravascular ultrasonographic follow-up at 6 months or 12 months. Optical coherence tomography was done in some patients. All patients were recommended to take dual antiplatelet therapy for at least 12 months. This trial is registered with ClinicalTrials.gov, number NCT01168830.

Findings Overall device and procedural success was 100%. Two of 46 (4%) patients had target lesion failure at 6 months (both clinically driven target lesion revascularisations), which rose to three of 43 (7%) at 12 months (one periprocedural target vessel myocardial infarction occurred during angiography at the 12 month follow-up visit). We noted no cardiac death or scaffold thrombosis.

Interpretation Our results show feasibility, a good safety profile, and promising clinical and angiographic performance results up to 12 months for DREAMS. Our promising clinical results show that absorbable metal scaffolds might be an alternative to polymeric absorbable scaffolds.

Funding Biotronik.

BIOSOLVE-I study results

Six to 36-month clinical follow-up

BIOSOLVE-I

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

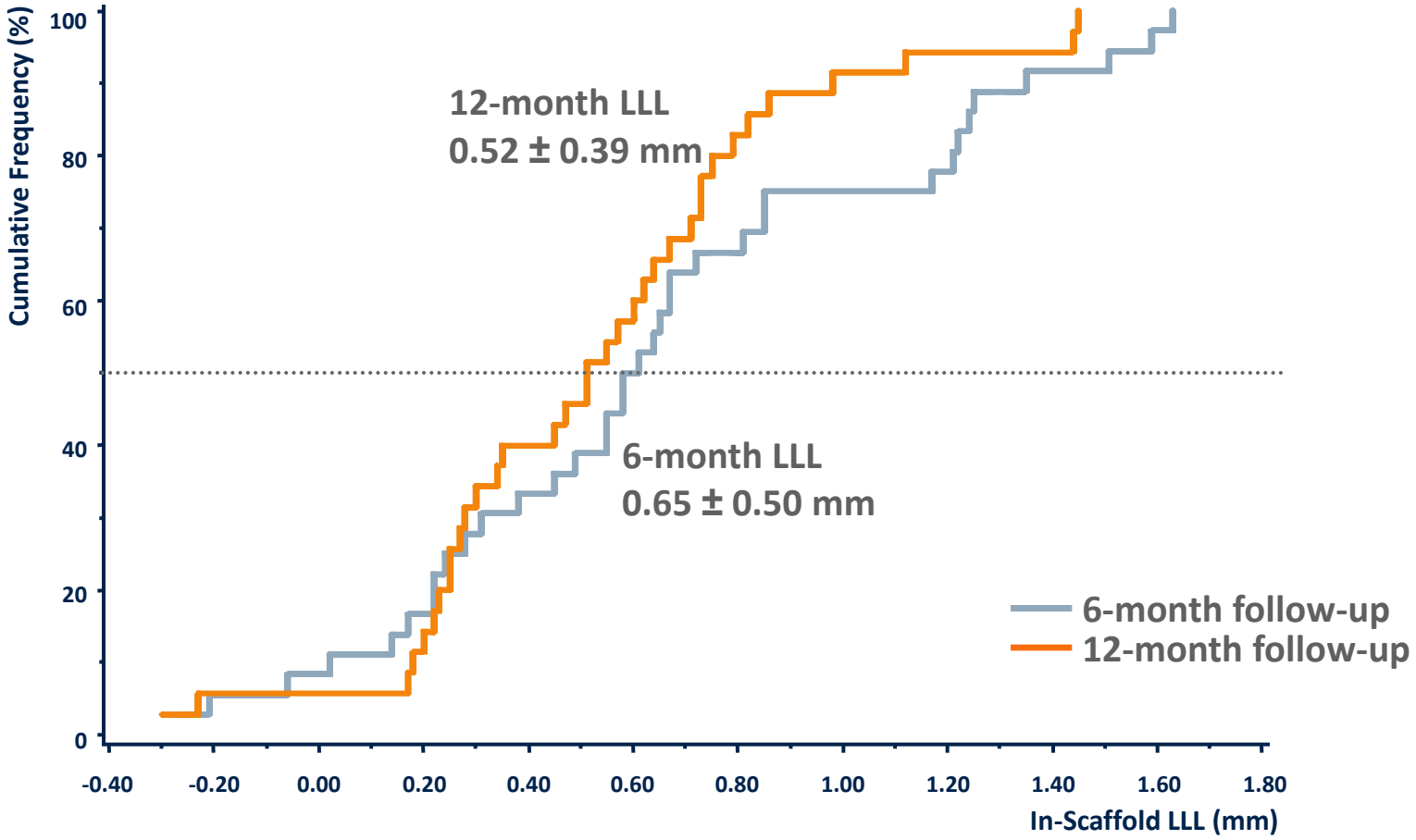
Clinical results	6-month[1]	12-month[1]	24-month[4]	36-month[4]
				Cohort 1
	N=46	N=44	N=44	N=20
TLF	2	3	3	2
Cardiac death	0	0	0	0
MI	0	1[2]	1[2]	0
Scaffold thrombosis	0	0	0	0
TLR[3]	2	2	2	2

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

BIOSOLVE-I study results

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

BIOSOLVE-I



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

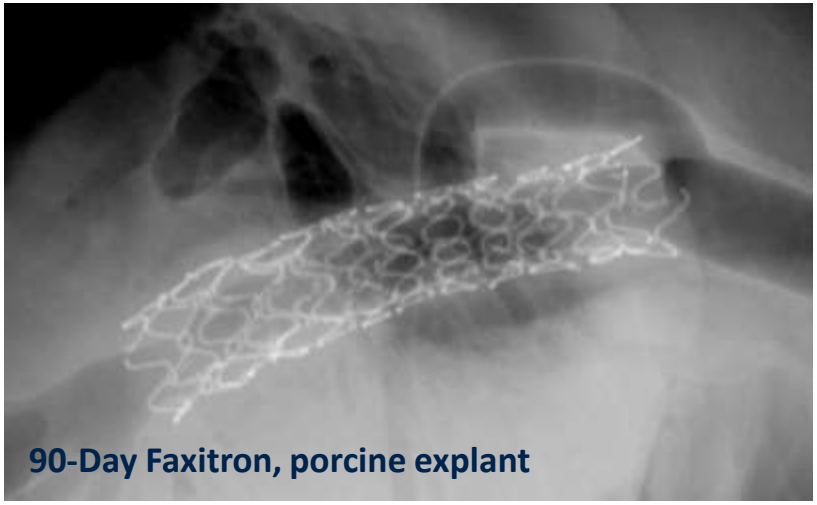
DREAMS Device Evolution (G1 → G2)

DREAMS G1

120µm

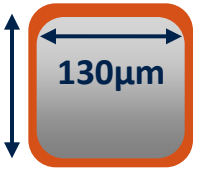
Drug: Paclitaxel

Polymer: PLGA



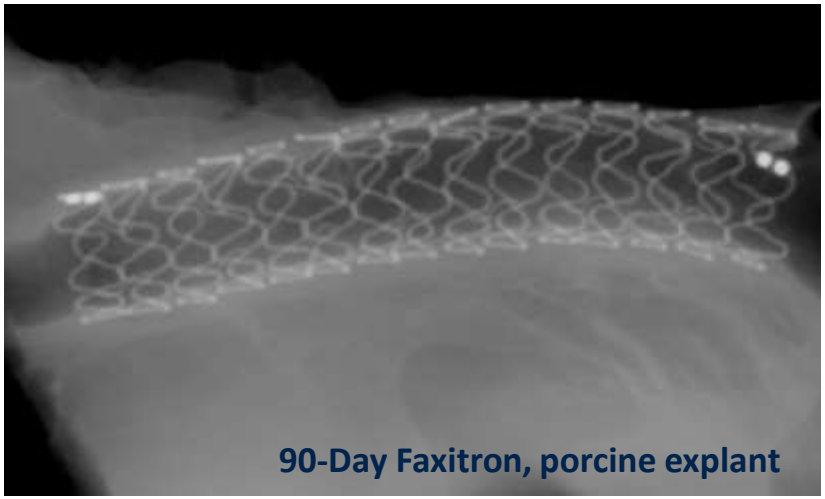
DREAMS G2

150µm



Drug: Sirolimus

Polymer: PLLA (BIOlute)



Source: BIOTROINK AG, data on file.

Key Summary of BRS Trials

Table 4 Summary of clinical trials with bioresorbable scaffolds

Scaffold	Clinical study	Number of patients	Major endpoints	Late loss (mm)	TLR	MACE
Metallic						
AMS-1	PROGRESS-AMS	63	MACE at 4 months	1.08 at 4 months	24% at 4 months	24% at 4 months
DREAMS-1	BIOSOLVE-I	46	Target lesion failure at 6 and 12 months	0.64 at 6 months 0.52 at 12 months	4.3% at 6 months 6.5% at 12 months	4.3% at 6 months 6.5% at 12 months
Polymeric						
Igaki-Tamai	Igaki-Tamai study	15	Acute recoil, late loss, and MACE at 6 months	0.48 at 6 months	6.7% at 6 months	6.7% at 6 months
BVS 1.0	ABSORB Cohort A	30	Acute success, MACE up to 5 years	0.44 at 6 months	0% at 6 months, 0% at 5 years	3.3% at 6 months, 3.4% at 5 years
BVS 1.1	ABSORB Cohort B	101	LLL, TLR, and MACE at 6 months, 1, 2, and 3 years	0.19 at 6 months 0.27 at 12 months	3.6% at 12 months	9% at 2 years 10% at 3 years
DESolve	DESolve 1	15	LLL at 6 months	0.19 at 6 months	6.7% at 12 months	20% at 12 months
	DESolve NX	120	Procedural success, LLL at 6 months, and MACE up to 5 years	0.21 at months	1.6% at 6 months	3.25% at 6 months
REVA	RESORB	27	MACE	1.81 at 6 months	66.7% at 6 months	
ReZolve	RESTORE	50	TLR at 6 months, LLL at 12 months	0.20 at 12 months for $n = 8$	2 of 12 at 6 months	2 of 12 at 6 months

LLL, late lumen loss; MACE, major adverse cardiac events; TLR, target lesion revascularization.

Eur Heart J. 2014 Mar;35(12):765-76

Limitations of DES Platforms

Strut and Coating Thickness In Perspective

Durable Polymer Coated Stents		Bioabsorbable Polymer Coated Stents			Bioabsorbable Stent
Xience CoCr-EES Promus PtCr-EES	Resolute CoNi-ZES	Biomatrix 316L-BES	Nobori 316L-BES	SYNERGY PtCr-EES	BVS PLLA-EES

Strut Thickness					
81µm	89µm	120µm	125µm	74µm	150µm
Polymer Coating					
Conformable 7-8µm / side	Conformable 6µm / side	Abluminal 11µm	Abluminal 20µm	Abluminal 4µm	Conformable 3µm / side

Unresolved Limitations of Bioabsorbable Stent

- High profile; type A lesions
- Complex lesions; Calcified or tortuous, LM, long, bifurcation
- Stretchability and fracture
- Overlapping
- Side branch
- Relatively high late loss

ABSORB II RCT

501 patients

Randomized 2:1 Absorb (N=334) vs. XIENCE PRIME (N=167)
Up to 40 European sites

Study Objective	**Compare safety, efficacy and performance of BVS vs. XIENCE PRIME** **FPI 28-Nov-2011**
Co-primary Endpoints	• **Vasomotion** assessed by change in angiographic MLD between pre- and post-nitrate at 3 years (superiority) • **MLD** at 3 years post nitrate minus angiographic MLD post procedure post nitrate (non-inferiority, reflex to superiority)
Treatment	**Up to 2 *de novo* lesions in different epicardial vessels** **Planned overlapping allowed in lesions ≤ 48 mm**
Device Sizes	**Scaffold diameters: 2.5, 3.0, 3.5 mm** **Scaffold lengths: 12**, 18, 28 mm**

*** Sizes to be introduced into the trial once available.*

A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease caused by de-novo native coronary artery lesions (ABSORB II): an interim 1-year analysis of clinical and procedural secondary outcomes from a randomised controlled trial

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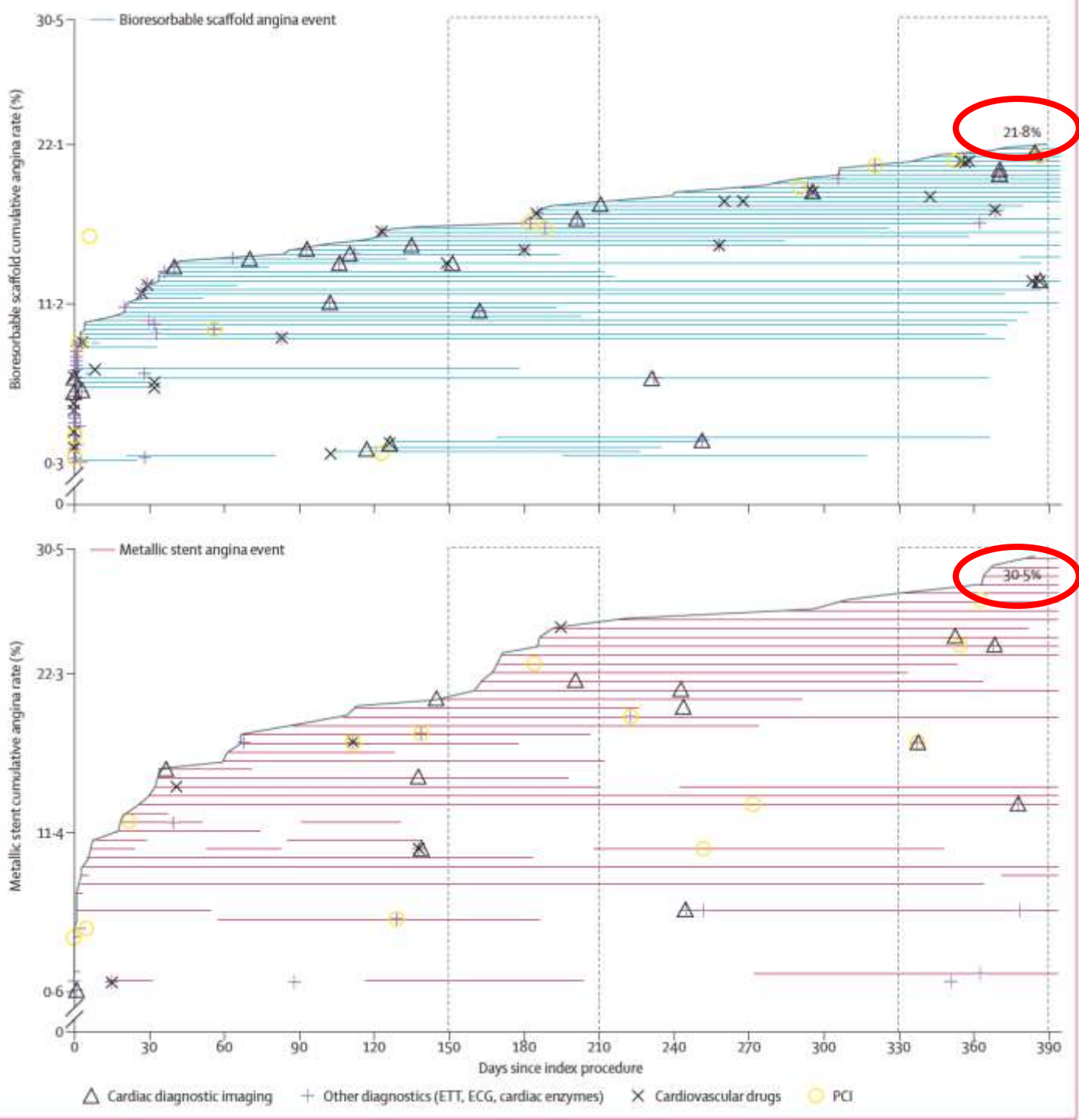
Lancet. 2014 Sep 12. [Epub ahead of print]

Cumulative rates of first new or worsening angina



	Bioresorbable scaffold group (n=335)	Metallic stent group (n=166)	Difference (95% CI)†	p value
Outcomes				
All deaths	0	1 (1%)	−0·61% (−3·35 to 0·65)	0·33
Cardiac deaths	0	0	0·00% (NA)	1·00
Myocardial infarction per protocol	15 (4%)	2 (1%)	3·32% (−0·25 to 6·26)	0·06
Q-wave	2 (1%)	0	0·60% (−1·71 to 2·18)	1·00
Non-Q-wave	13 (4%)	2 (1%)	2·72% (−0·78 to 5·53)	0·16
All target-lesion revascularisation	4 (1%)	3 (2%)	−0·61% (−4·08 to 1·60)	0·69
Clinically indicated target-lesion revascularisation	4 (1%)	3 (2%)	−0·61% (−4·08 to 1·60)	0·69
All target-vessel revascularisation	8 (2%)	8 (5%)	−2·43% (−7·01 to 0·86)	0·15
Clinically indicated target-vessel revascularisation	6 (2%)	6 (4%)	−1·82% (−6·01 to 1·04)	0·23
Non-clinically indicated target-vessel revascularisation	3 (1%)	3 (2%)	−0·91% (−4·35 to 1·19)	0·40
Non-target-vessel revascularisation	6 (2%)	6 (4%)	−1·82% (−6·01 to 1·04)	0·23
Clinically indicated non-target-vessel revascularisation	5 (1%)	4 (2%)	−0·91% (−4·66 to 1·55)	0·49
Non-clinically indicated non-target-vessel revascularisation	3 (1%)	2 (1%)	−0·31% (−3·46 to 1·63)	1·00
All revascularisation	12 (4%)	12 (7%)	−3·65% (−8·89 to 0·37)	0·08
Clinically indicated revascularisation	9 (3%)	9 (5%)	−2·74% (−7·50 to 0·75)	0·12
Non-clinically indicated revascularisation	6 (2%)	5 (3%)	−1·22% (−5·21 to 1·49)	0·52

Composite secondary endpoints				
Cardiac death, all myocardial infarction, clinically indicated target-vessel revascularisation (target-vessel failure)	18 (5%)	8 (5%)	0·59% (–4·26 to 4·41)	0·78
Cardiac death, target-vessel myocardial infarction, and clinically indicated target-lesion revascularisation (target-lesion failure; device-oriented composite endpoint)	16 (5%)	5 (3%)	1·80% (–2·48 to 5·16)	0·35
Cardiac death, all myocardial infarction, and clinically indicated target-lesion revascularisation (major adverse cardiac events)	17 (5%)	5 (3%)	2·11% (–2·20 to 5·51)	0·28
All death, all myocardial infarction, and all revascularisation (patient-oriented composite endpoint)	24 (7%)	15 (9%)	–1·84% (–7·69 to 2·98)	0·47
Thrombosis endpoints				
Definite scaffold or stent thrombosis	2 (0·6%)	0	0·61% (–1·72 to 2·19)	1·00
Acute (0–1 day)	1 (0·3%)	0	0·30% (–1·98 to 1·67)	1·00
Sub-acute (2–30 days)	1 (0·3%)	0	0·30% (–1·98 to 1·68)	1·00
Late (31–365 days)	0	0	0·00% (NA)	1·00
Definite or probable scaffold or stent thrombosis	3 (0·9%)	0	0·91% (–1·45 to 2·65)	0·55

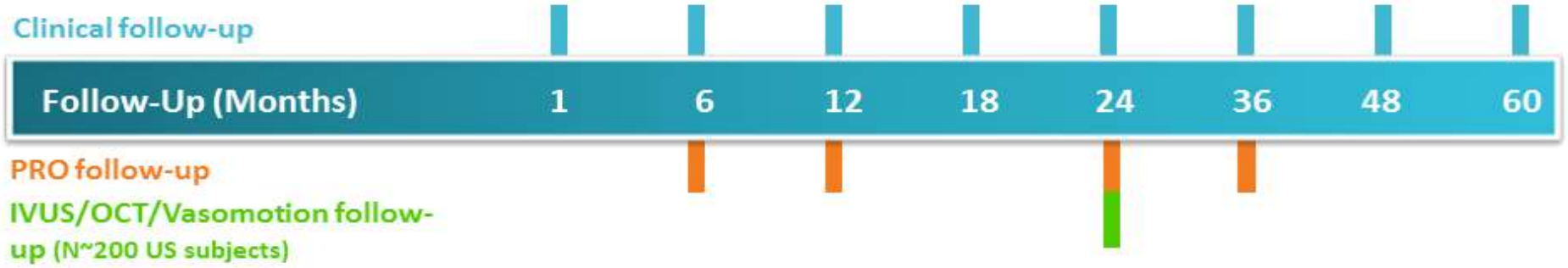
Data are n (%).

Table 5: Secondary clinical outcomes at 1-year follow-up

ABSORB III: US Approval RCT

NON-inferiority at One YEAR vs DES

~2000 subjects (1267 Absorb, 733 XIENCE)
US and Australian sites. Follow-up out to 5 years



Study Objective	Seek US approval of Absorb BVS
Primary Endpoint	Clinically indicated target lesion failure at 1-year (composite of cardiac death, target vessel MI or clinically indicated TLR)
Treatment	Up to two *de novo* lesions in different epicardial vessels. No planned overlap allowed
Device Sizes	Scaffold diameters: 2.5, 3.0, 3.5 mm Scaffold lengths: 12, 18, 28 mm

ABSORB IV

~3,000 pts randomized 1:1 ABSORB v XIENCE

RVD: 2.50 - 3.75 mm; Lesion length: ≤24 mm

Scaffold diameters: 2.5, 3.0 and 3.5 mm
Scaffold lengths: 12, 18, and 28 mm

~5,000 total pts (ABSORB III + IV) with up to 2 de novo lesions in different epicardial vessels randomized, with FU for at least 5 years, at up to 160 US and non-US sites

Primary endpoints:

1. Angina at 1 year (ABSORB IV)
2. TLF between 1 and 5 years (landmark analysis)

Future Perspectives on BVS Research

- ***Stable CAD***
  - BRS vs. newer generation DES
    - At least equivalent efficacy and safety
    - Extension of results to more complex lesions/patients
  - BRS vs. medical treatment in symptomatic CAD
- ***ACS***
  - BRS vs. newer generation DES in culprit lesions
  - BRS vs. medical treatment in non-culprit lesions
- ***Diabetic Patients***
  - BRS vs. newer generation DES
- ***Device Performance and Antiplatelet Therapy***
  - Investigate optimal antiplatelet regimens