Interventional Innovation I: Coronary Interventions and Technologies

Sirolimus Angioplasty Balloon for In-Stent Restenosis (SABRE) Trial: 3-Year Clinical Follow-Up

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On Behalf of SABRE Investigators

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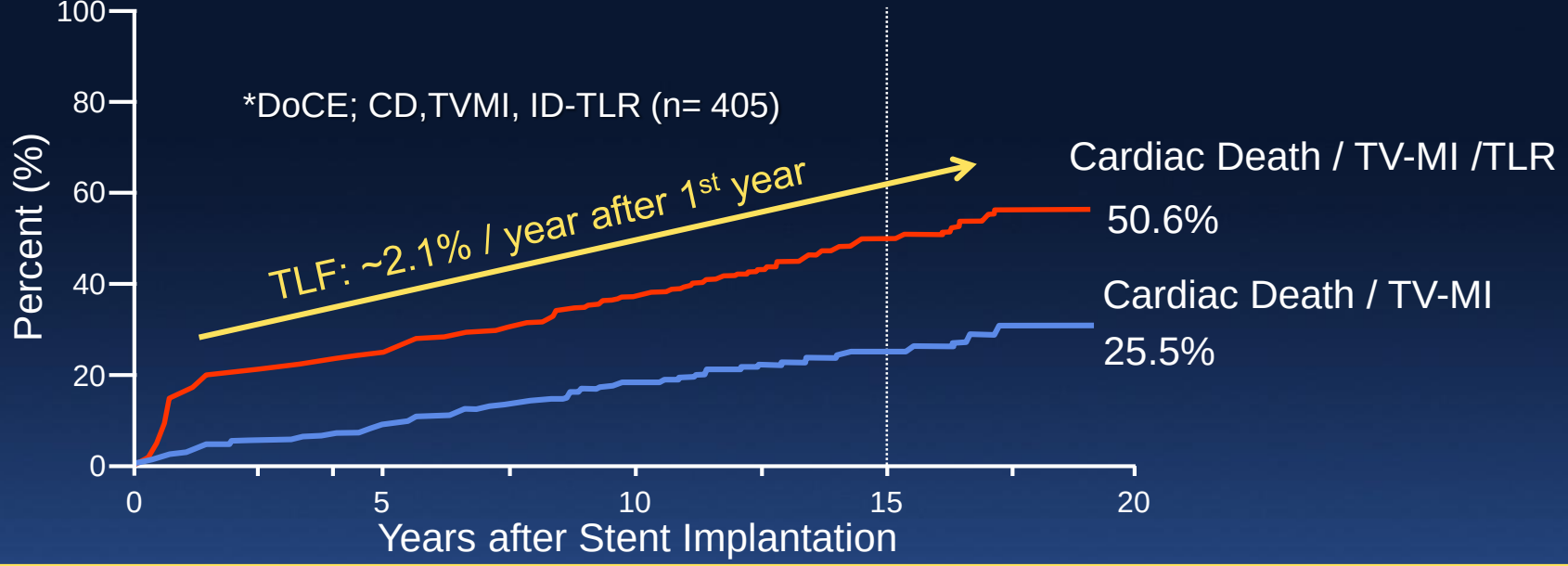
tct2018

Cardiovascular Research Foundation

Disclosure Statement of Financial Interest

- I, Juan F. Granada DO NOT have a personal financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation
- Caliber therapeutics has performed sponsored clinical at the Cardiovascular Research Foundation within the last 12 months

Very Late Adverse Events* Following BMS Implantation: 15-Year Follow-Up (1990-1993)



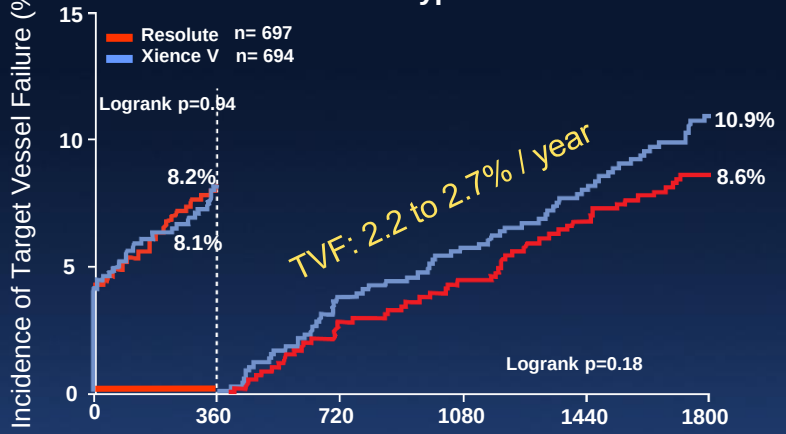
High restenosis rates at 6 months
Target Lesion Failure (TLF)* continues to accrue at ~2.1% annual rate

Yamaji K et al. Circ CV Int. 2010;3:468-475

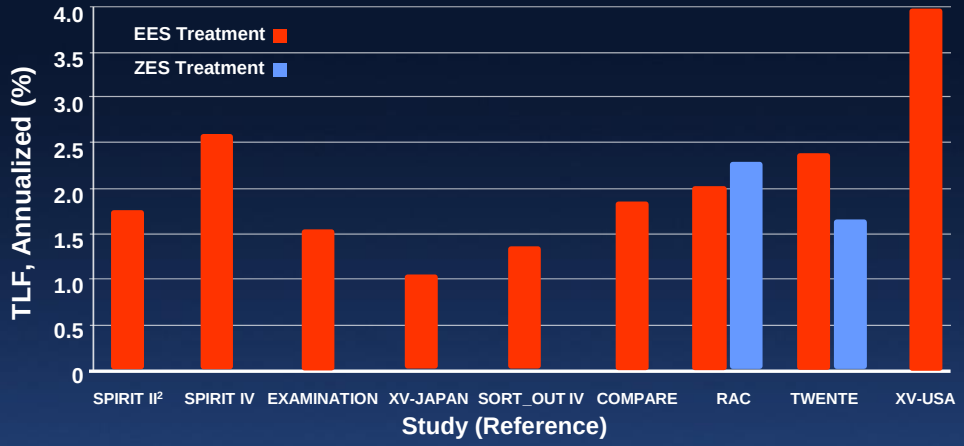
5-Year TVF Following DES Implantation

Late Events Likely Related to the Permanent Presence of the Metal Stent or Polymers

Target Vessel Failure Through 5 Years by Randomized Stent Type TWENTE Trial[1]



Annualized Percentage of Target Lesion Failure (TLF) Beyond 1 Year by Device and Study[2]



DES improved short-term (1-year) TLR & clinical outcomes

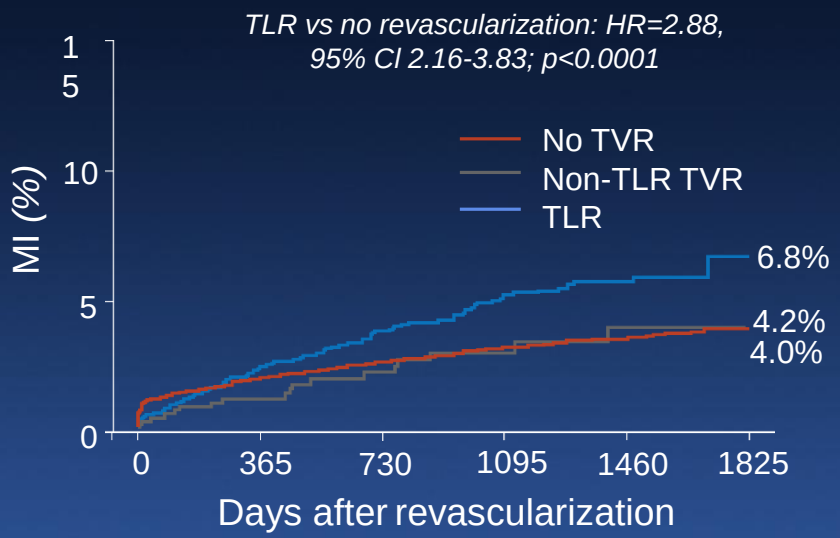
~2% to 4% annual incidence of TLF at 5 years with the latest generation DES

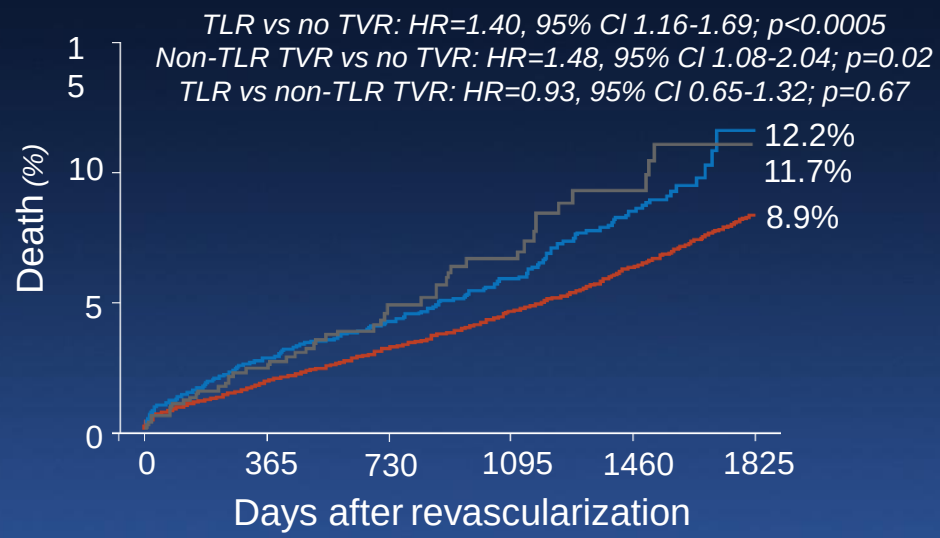
[1]Von Birgelen et al. JAMA Cardiology 2017. [2]Kereiakes. JAMA 2017

Re-Intervention is Associated to Long-Term Increase in MI & Death

Patient Data Pooled Analysis of 21 RCT /32,500 Patients

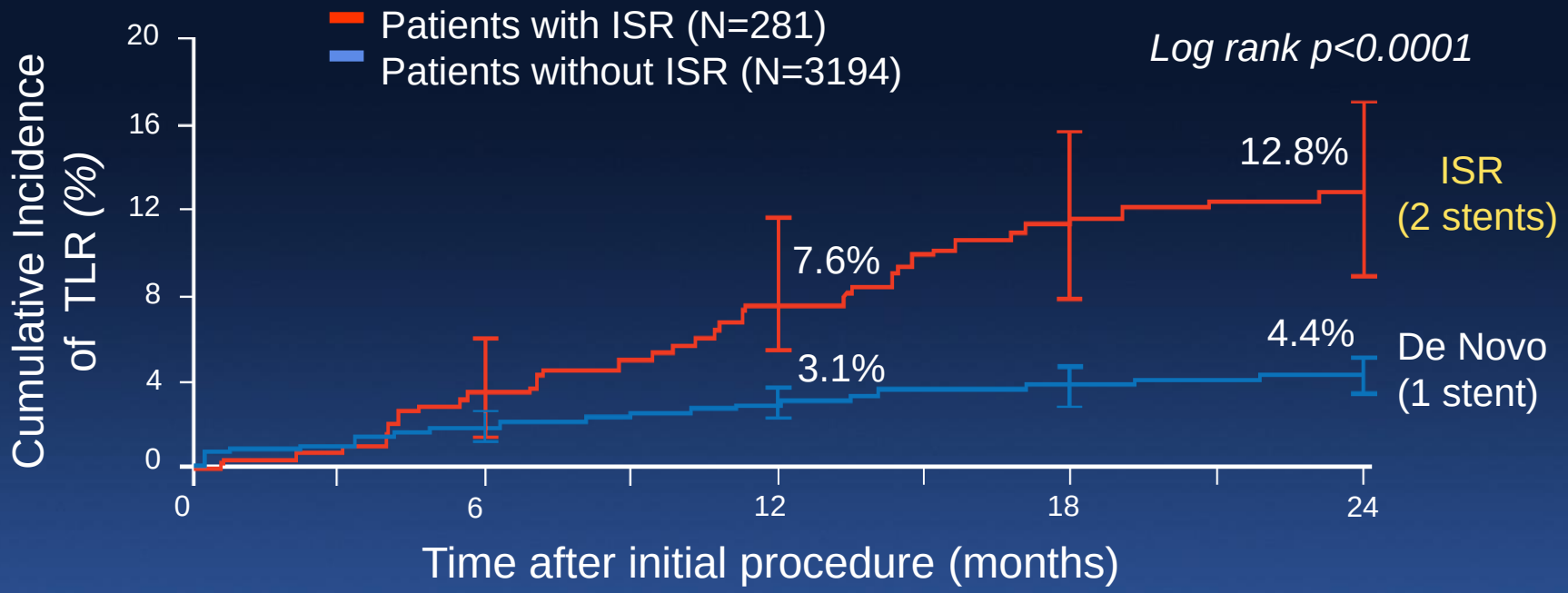
Non-Emergent, Uncomplicated TLR





Palmerini et al.– JACC Card Inter 2018

An Additional Stent Layer is Associated to Worse Long-Term Clinical Outcomes



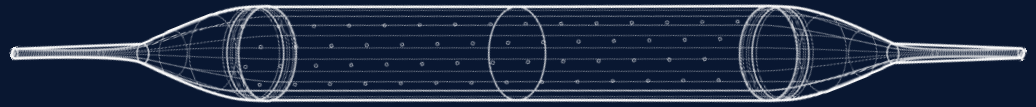
Richardt et al. JACC Cardiov Inter 2013

Balloon-Based Sirolimus Delivery

Design Requirements

- Dose uniformity and reliability is compromised by inefficient drug transfer from balloon surface; **a dedicated delivery mechanism is required**
- Tissue absorption is **limited** following acute drug transfer:
  - Sirolimus **degradation / diffusion** occurs; **"drug protection"** (i.e., encapsulation) is needed
  - Sirolimus half life is short (~62-hours) and biological effect depends on maintaining therapeutic levels **(sustained and controlled drug delivery favored)**
- Distal **embolization** must be minimized or eliminated

Virtue® Sirolimus-Eluting Balloon



Micro-Porous Angioplasty System

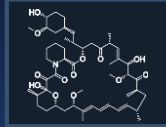
Compliance of POBA and NO COATING

Particle Delivery Technology

ENHANCED tissue penetration

PROTECTION from rapid elution

CONTROLLED and sustained release



Sirolimus

- Proven clinical data for treatment of coronary atherosclerosis
- ALL leading drug-eluting stents (DES) utilize “limus” analogs

Bioresorbable Particle Delivery Technology

- Enables sustained delivery of sirolimus
- Pharmacokinetics comparable to proven DES
- Passes critical particulate testing, a key safety metric

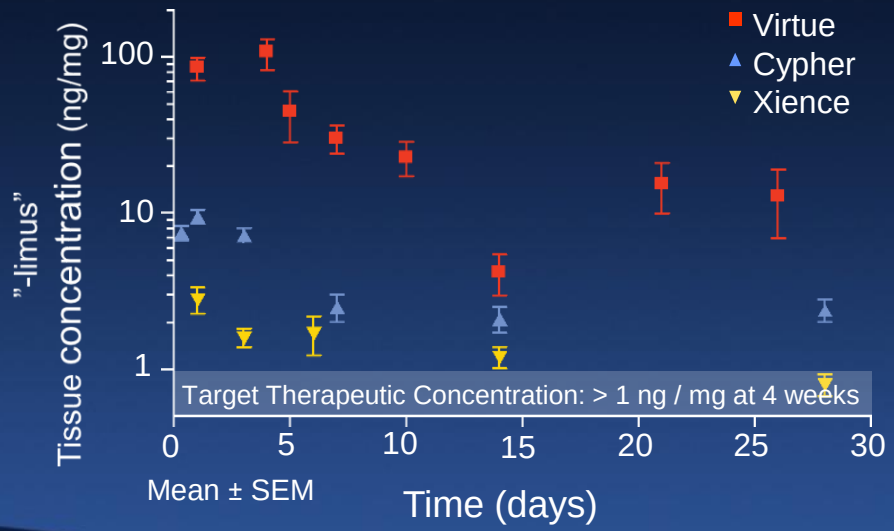
Micro-Porous Angioplasty System

- Performance equivalent to standard balloon angioplasty
- Delivers programmed dosage of drug-loaded particles to target lesion with minimal downstream, off-target effects

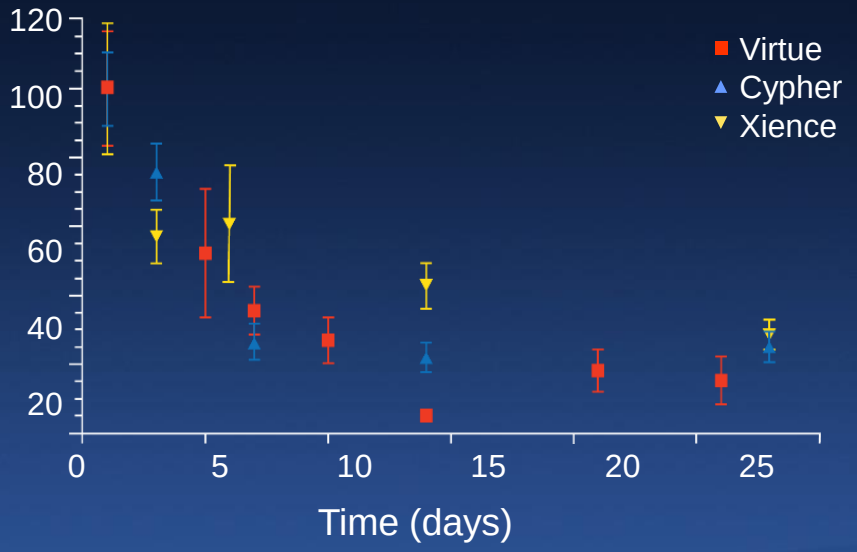
Virtue® SEB vs. Limus-Eluting Stent

Bioresorbable particle delivery technology designed to achieve tissue concentrations of sirolimus compared to clinically proven DES[1]

Arterial Tissue Concentration



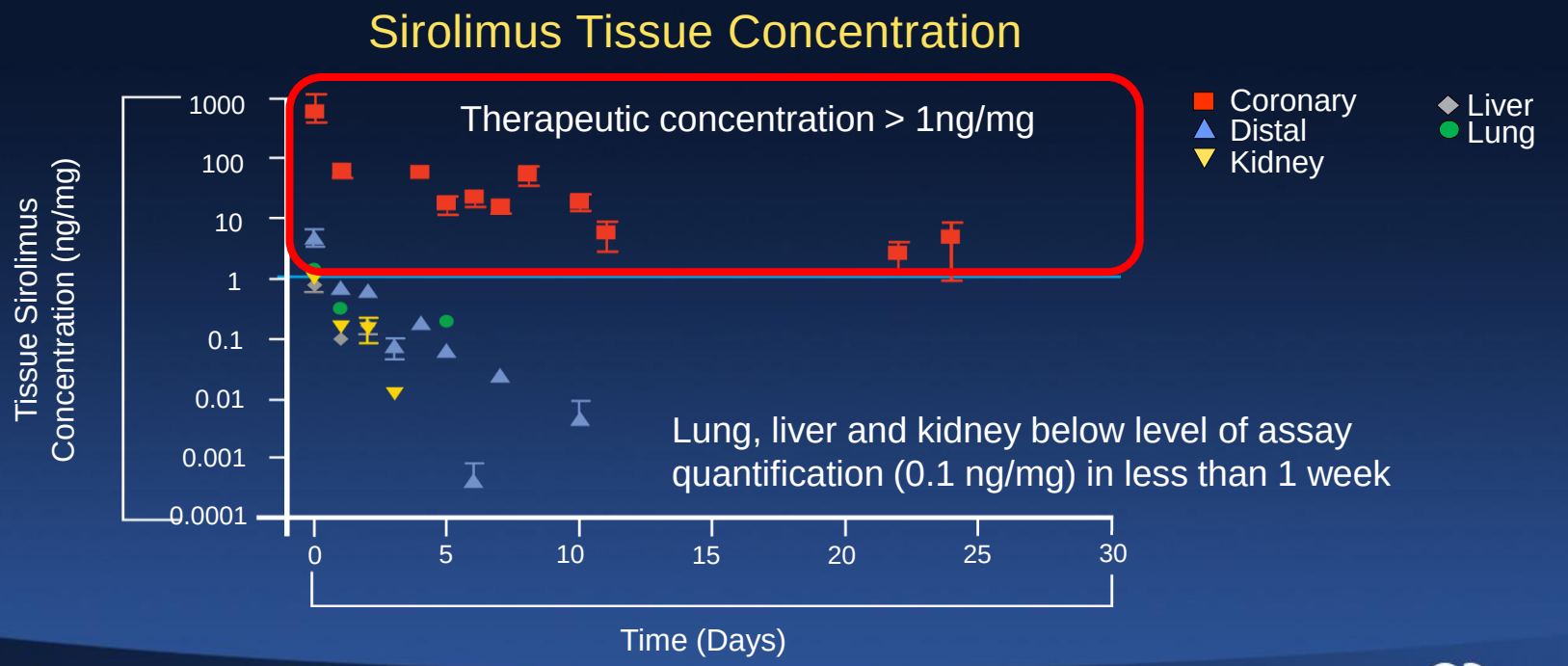
Normalized Tissue Kinetics



[1]Granada J, et al. EuroIntervention 2016;12:740-747

Virtue® SEB: Targeted Drug Delivery

Sirolimus arterial tissue concentration at target treatment site is >300-fold higher compared to off-target systemic drug levels



[1]Granada J, et al. EuroIntervention 2016;12:740-747

SABRE – Coronary ISR Study

Study Title	Sirolimus Eluting Angioplasty Balloon for In-Stent Restenosis, SABRE
Study Design	Prospective multi-center study evaluating a Drug Eluting Balloon in patients undergoing percutaneous revascularization of coronary in-stent restenosis for separate BMS ISR and DES ISR subgroups
Number of Subjects	50
Primary Endpoint	Safety: Target Lesion Failure (TLF) Composite of cardiac death, target vessel MI and clinically driven target lesion revascularization up to 30 days post index procedure. Efficacy: In-Segment Late Lumen Loss (LLL) at 6 month Follow Up Assessed by Quantitative Coronary Angiography (QCA) and adjudicated by an independent Angiographic Core Lab
Subject Duration	Each subject is expected to be enrolled in the study for 36 months
Principal Investigator	Dr. Stefan Verheye
Sites	9 sites in Belgium, Netherlands, Denmark and Latvia
Trial Coordinator (CRO)	Genae associates nv
Core Lab, CEC & DSMB	CRF

Verheye S. JACC Cardiovasc Interv. 2017; 10: 2029-37

SABRE: Baseline Characteristics

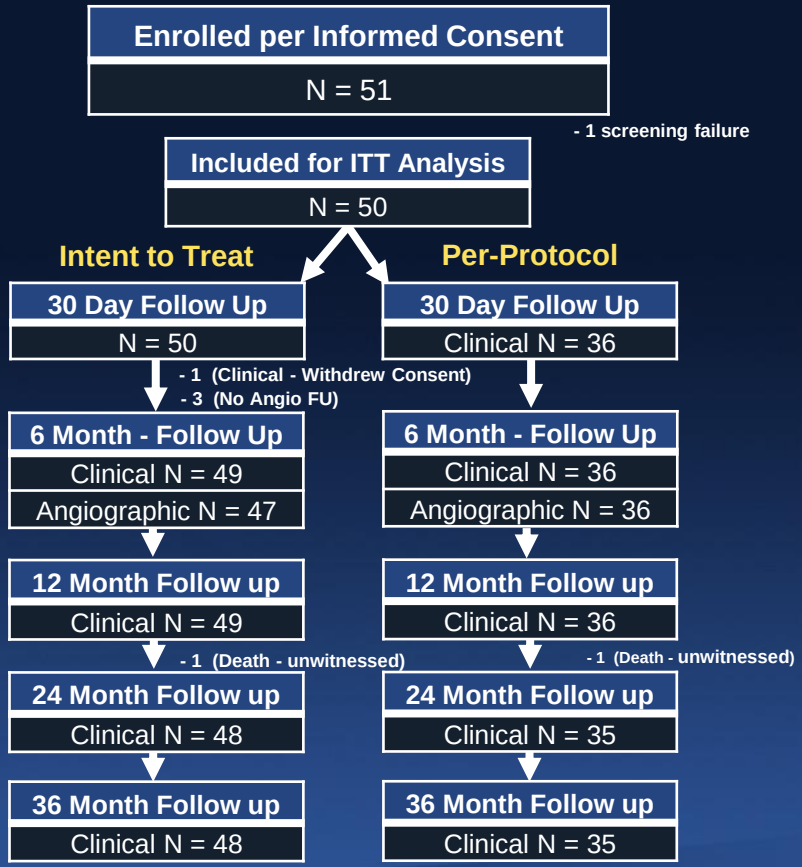
Baseline Characteristics (ITT Population)	
n	50
Age	68 ± 9.5
Male	80%
Diabetes	18%
Hypertension	74%
Hyperlipidemia	74%
Smoking (Previous and Current)	70%
Previous MI	56%
Renal Insufficiency	8%
BMS ISR / DES ISR	32 / 18
Time from Previous PCI (Years)	3.9 ± 4.7

Procedural Characteristics (ITT Population)	
Target-Vessel Location	
LAD	25 (50%)
Baseline Measurements	N = 50
Lesion Length, mm	13.0 ± 4.1
Stent Length, mm	20.9 ± 10.2
Stent diameter, mm	3.14 ± 0.35
RVD*, mm	2.61 ± 0.39
MLD, mm	0.83 ± 0.31
Diameter Stenosis*, %	68.1 ± 11.4
Diffuse Pattern (Mehran Classification)	62% (31)
Virtue™ Sirolimus Eluting Balloon	
Length (mm)	17.3 ± 3.5
Diameter (mm)	3.18 ± 0.30
Inflation pressure (Atm)	14.2 ± 2.7
Inflation time (Sec)	39.8 ± 9.7
Post-Index Procedure	
RVD (mm)	2.55 ± 0.39
MLD (mm)	2.08 ± 0.32
Diameter Stenosis (%)	17.7 ± 9.2
Bailout Stent	3 (6%)

Verheye S. JACC Cardiovasc Interv. 2017; 10: 2029-37

SABRE: Subject Disposition

- 14 Subjects excluded from Per Protocol Analysis (PP)
  - The independent Angiographic Core Lab (CRF) evaluated all major protocol violations
  - 11 subjects excluded from based on core lab measurements:
    - Ostial or major side branch lesions
    - Additional lesions in target vessel
    - Lesion significantly outside stent edges
    - Lesions longer than available balloons
  - 3 subjects with prior DES treated ISR excluded to eliminate confounding factors (i.e., multiple stent layers and/or drug treatments



Verheye S. JACC Cardiovasc Interv. 2017; 10: 2029-37

SABRE: Angiographic Results at 6 Months

Biologic Efficacy Consistent with Therapeutic Delivery of Sirolimus Despite Complex and Challenging Cases

SABRE Angiographic Results – 6 months		
	Intent to Treat	Per Protocol
Number of Patients	50 / 47	36
Reference Vessel Diameter (RVD) mm **	2.52 ± 0.38	2.52 ± 0.32
Minimum Lumen Diameter (MLD) mm	1.75 ± 0.54	1.96 ± 0.32
% Diameter Stenosis **	30.3 ± 19.9	22.3 ± 9.4
Change in % Diameter Stenosis **	12.7 ± 20.6	5.2 ± 11.4
Late Lumen Loss (LLL) mm*	0.31 ± 0.52	0.12 ± 0.33
Binary Restenosis #	19.1%	2.8%

** Trial primary performance endpoint, #Trial secondary performance endpoint, ** RVD reported using Internormal values*

Verheye S. JACC Cardiovasc Interv. 2017; 10: 2029-37

SABRE: Clinical Safety Outcomes to 3 Years

	Intent to Treat Analysis (ITT)						Per Protocol Analysis (PP)			
	In-Hospital	30 Days	6 Months	1 Year	2 Years	3 Years	6 Months	1 Year	2 Years	3 Years
n	50	50	49	49	49	49	36	36	36	36
Cardiac Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)**	1 (2.0%)**	0 (0.0%)	0 (0.0%)	1 (2.8%)**	1 (2.8%)**
TV-MI	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 2.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TLR	0 (0.0%)	0 (0.0%)	4 (8.2%)	6 (12.2%)	6 (12.2%)	6 (12.2%)	1 (2.8%)	1 (2.8%)	1 (2.8%)	1 (2.8%)
TLF	0 (0.0%)	0 (0.0%)*	4 (8.2%)	6 (12.2%)	7 (14.3%)	7 (14.3%)	1 (2.8%)	1 (2.8%)	2 (5.6%)	2 (5.6%)

**Primary safety endpoint is 30 day TLF. **Cause of death unknown - reported as multiple organ failure non cardiac and non-neurological. Adjudicated as non-device and non-procedure related.*

No MI during procedure – safe delivery of sirolimus formulation

No 30 day Major Adverse Cardiac Events (MACE) – primary endpoint

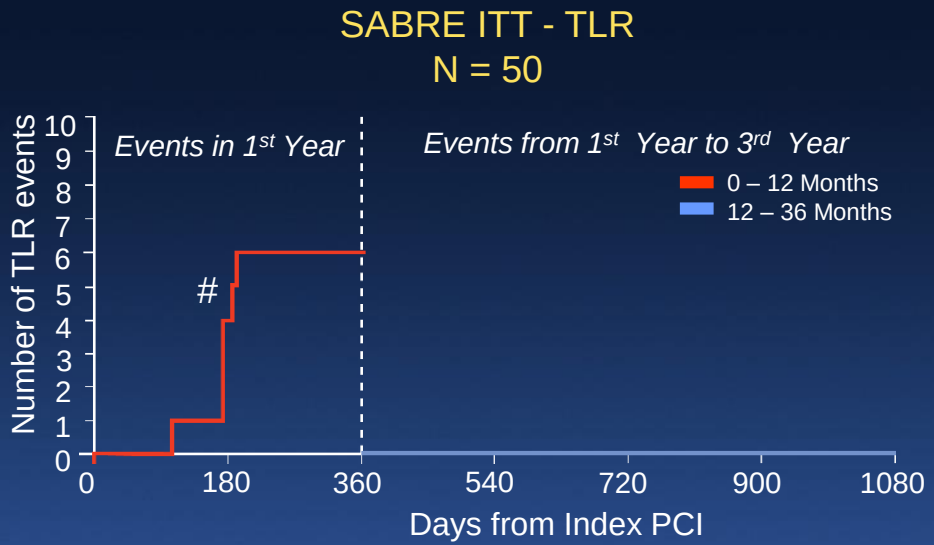
6 month, 1 year, 2 year and 3 year TLF rates comparable to clinically available technologies

No new revascularization events between 1 year and 3 years

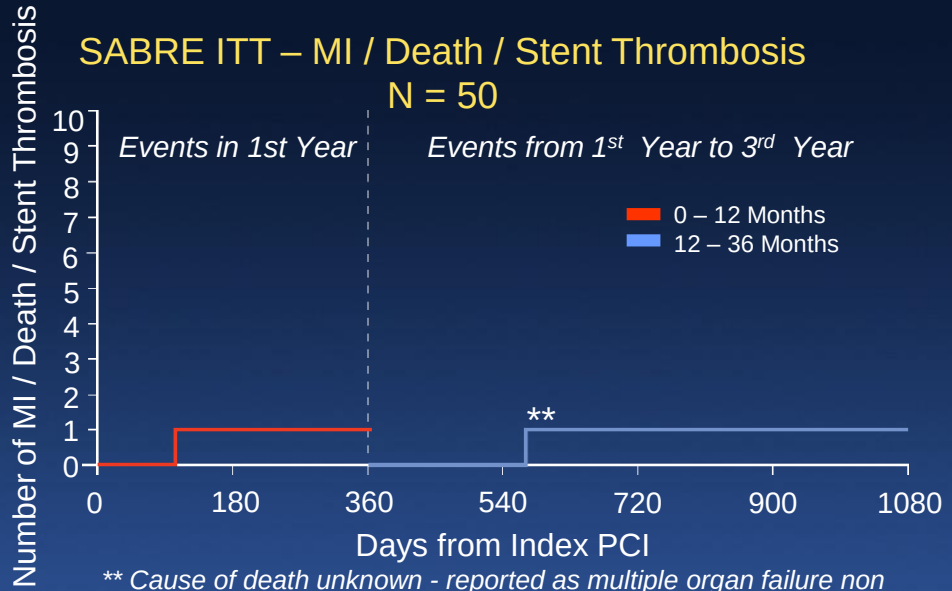
SABRE ITT Results Demonstrate Safety

No events in first 90 days and No TLR events beyond angiographic follow up

1 TV-MI in first year and 1 unknown cause death between year 1 and year 3



 # 5 TLR events occurred at time of 6 month angiographic follow up



*** Cause of death unknown - reported as multiple organ failure non cardiac and non-neurological. Adjudicated as non-device and non-procedure related.*

Virtue® SEB Compare Favorably to PCB's in Key Safety Measures

Coronary ISR PCB Trials: 12 Month Clinical Follow Up

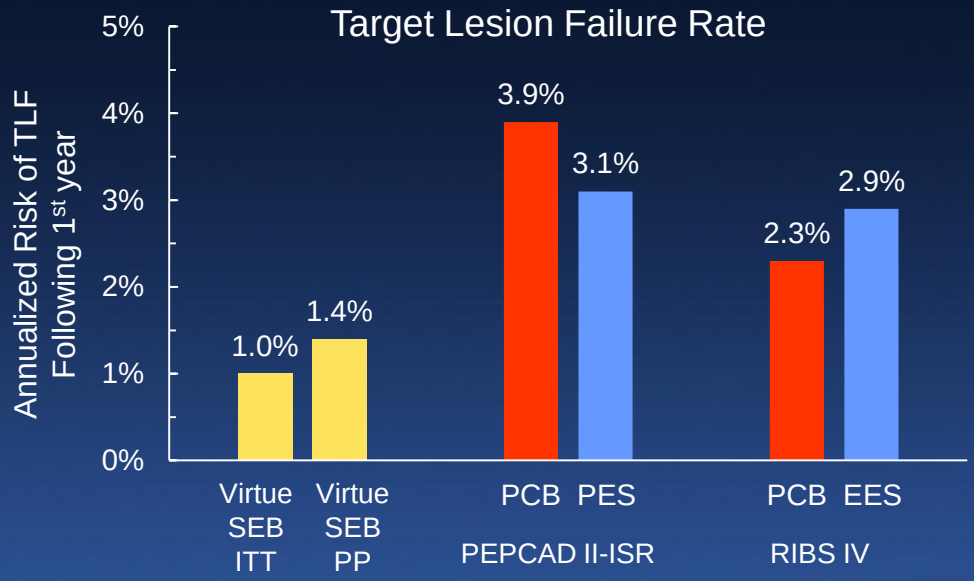
	Sirolimus Eluting Balloon		Paclitaxel Coated Balloon				
	Virtue[1]		B Braun SeQuent[2]	B Braun SeQuent[3]	Biotronic Pantera Lux[4]	BSC Agent[5]	Medtronic In.Pact[6] Registry
	ITT	**PP**					
N	49	36	154	137	148	65 / 59	428
Cardiac Death	0.0%	0.0%	1.3%	2.2%	2.0%	3.1%	1.3%
MI	2.0%	0.0%	3.2%	2.1%	5.5%	3.1%	4.3%
Thrombosis	0.0%	0.0%	NR	0.7%	0.0%	0.0%	NR

[1]Verheye et al. Virtue SABRE Trial JACC: Cardiovascular Interventions 2017. [2]Alfonso et al: RIVS IV JACC 2015. [3]Byrne et al: ISAR-DESIRE 3 Lancet 2013. [4]Jensen et al BIOLUX RCT Eurointervention 2018. [5]Nef et al. AGENT Trial PCR 2018 Widder et al. [6]FALCON-Registry Eurointervention 2018.

Annualized Risk: Virtue® SEB Data Favorable to Paclitaxel DCB

Virtue® SEB Compares Favorably to DES AND Paclitaxel DCB

Coronary In-Stent-Restenosis (ISR)		
SABRE[1]	Virtue® SEB ITT	Sirolimus - Eluting Balloon
	Virtue® SEB PP	
PEPCAD II – ISR[2]	SeQuent PCB	Paclitaxel - Coated Balloon
	PES	Paclitaxel - Eluting Stent
RIBS IV[3]	SeQuent PCB	Paclitaxel - Coated Balloon
	EES	Everolimus - Eluting Stent



[1]Virtue SABRE Trial: Verheye et al JACC: Cardiov Intervent 2017; [2]Unverdorben et al, PEPCAD II ISR Eurointervention 2014; [3] Alfonso et al: RIVS IV JACC 2015

SABRE Feasibility Study Summary

- The Virtue® SEB has demonstrated:
  - A sirolimus elution and safety profile similar to metallic DES
  - A clinical SAFETY and EFFICACY despite a challenging DES-ISR population
- The SABRE Trial showed:
  - Angiographic Late Loss: ITT 0.31-mm and PP: 0.12-mm
  - Clinical Outcomes:
    - ITT: 0.0% MACE in hospital and 14.3% TLF at 3 years
    - PP: 0.0% MACE in hospital and 5.6% TLF at 3 years
    - No TLR events (ITT) following 6 month angiographic assessment
    - 1 MACE between year 1 and year 3 (unwitnessed death)
- An IDE study in coronary ISR (SABRE PP population) is under development