EPC Capture Stent: A promising solution amongst the DAPT controversy?

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Mount Sinai Heart

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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. These relationships may lead to bias in my presentation.

Affiliation/Financial Relationship	Company
• Grant/Research Support (Institutional)	• The Medicines Co., AZ, BMS, Lilly/Daiichi Sankyo
• Advisory Board	• Janssen (J+J),
• Consulting Fees/Honoraria	• Janssen (J+J), Maya Medical,

Areas for Improvement with DES in 2016

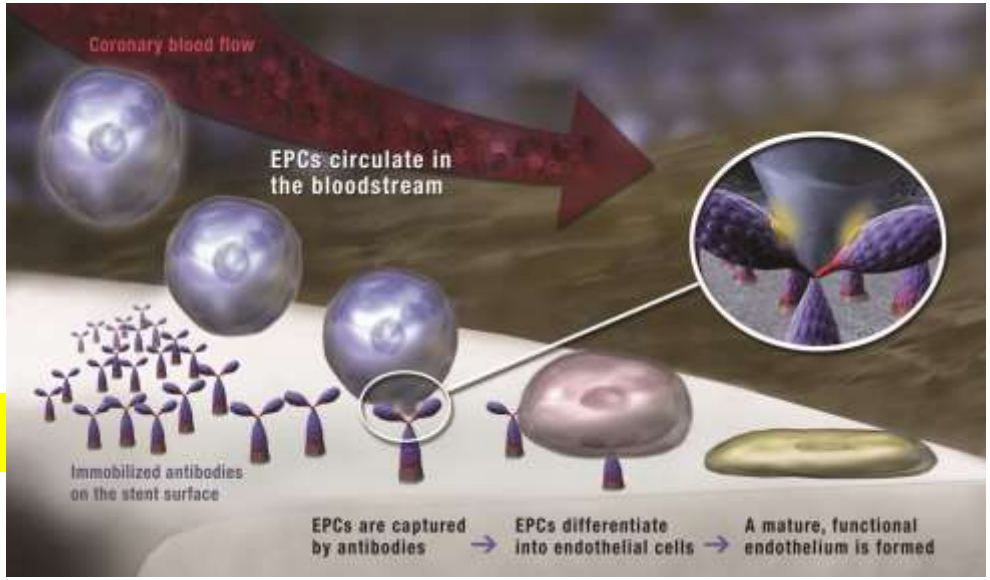
- First 30 day safety
- Early DAPT interruption
- Duration of DAPT
- Thrombotic lesions (ACS, STEMI)
- Long term healing

Components of Currently Available DES

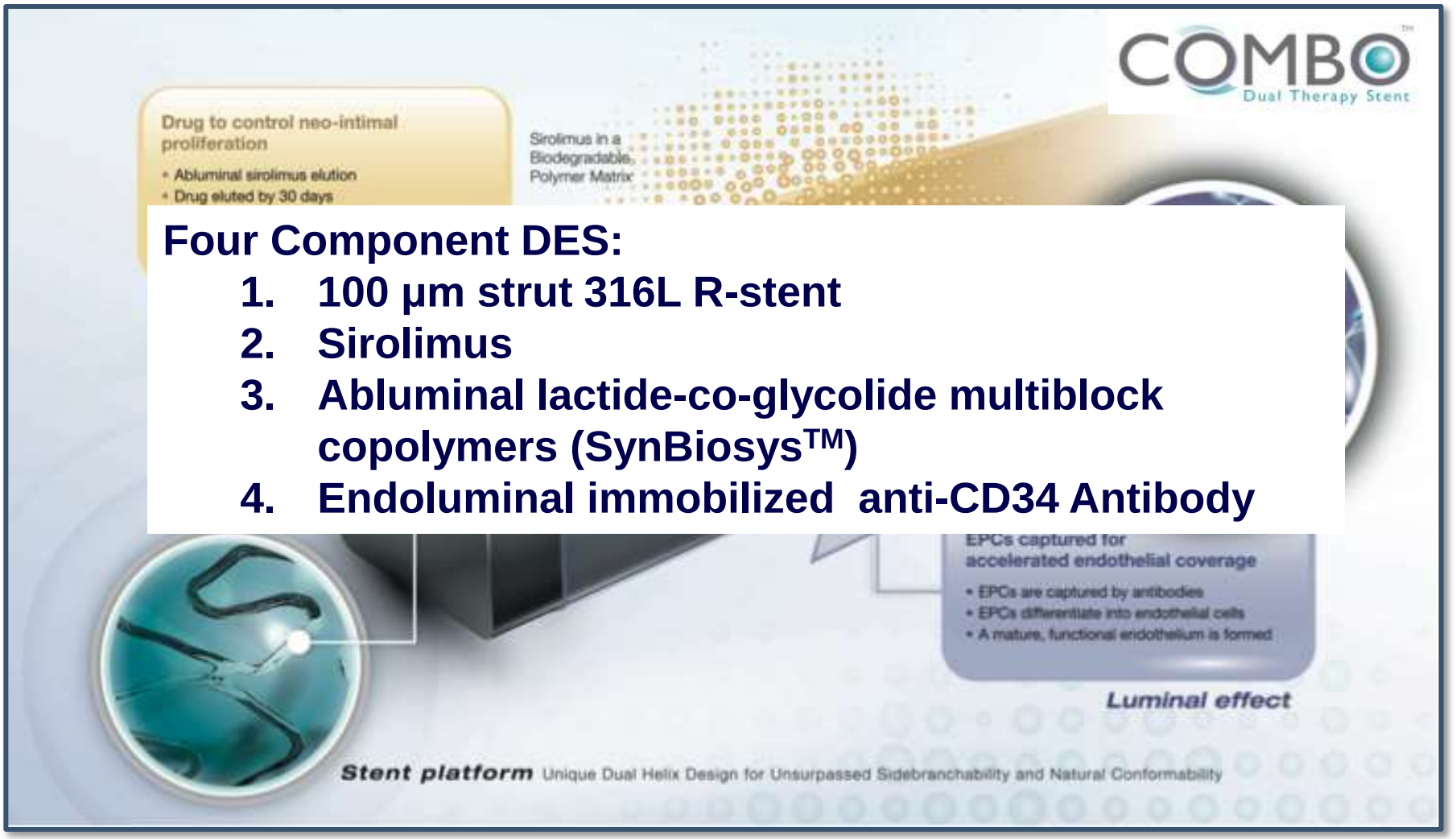
Dual Therapy Stent

- Scaffold Platform
- Anti-proliferative Drug
- Polymer (biodegradable)
- EPC Capture (pro-healing)

90 days



Luminal EPC Capture

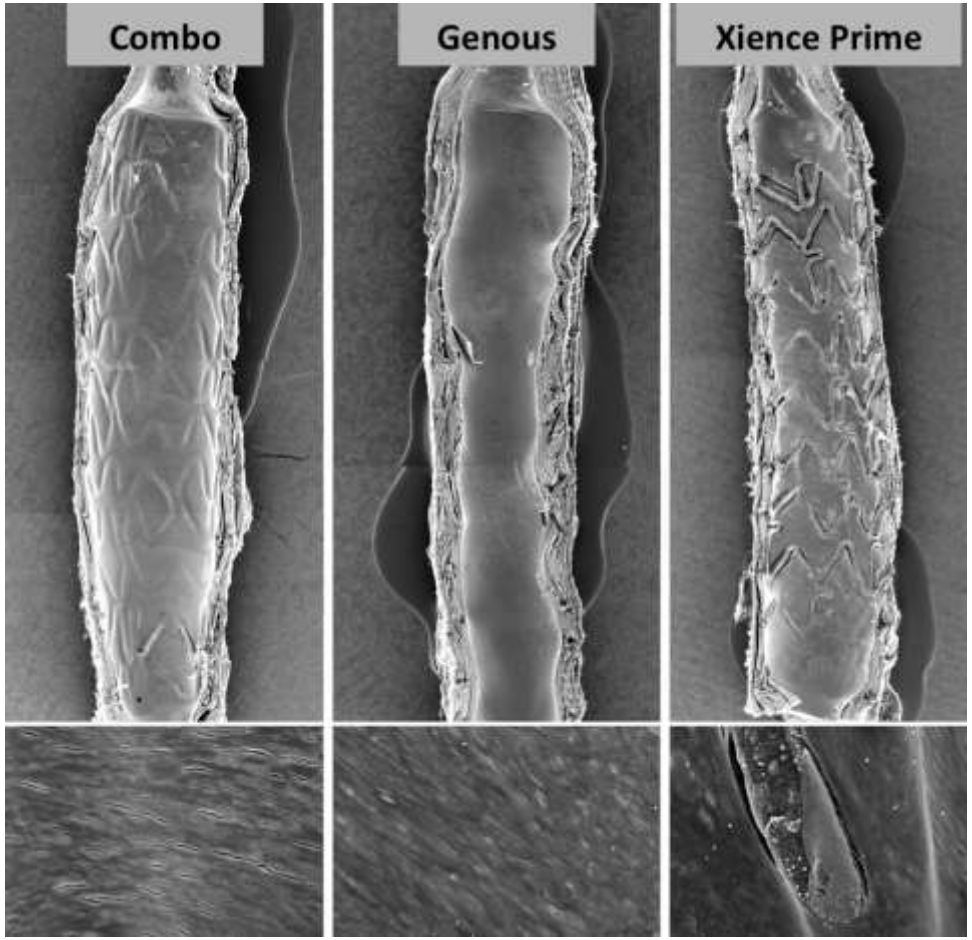


The first four component DES

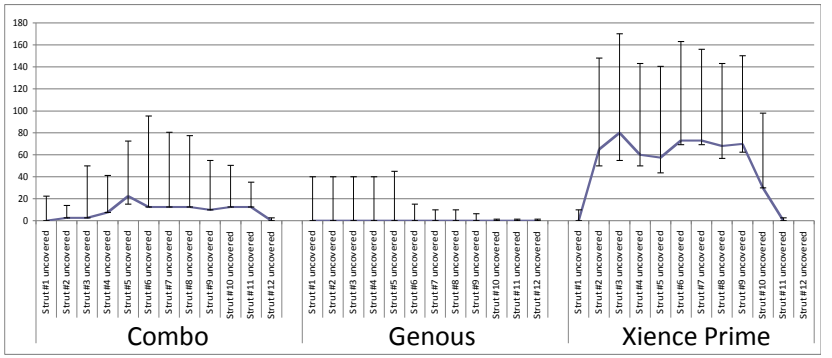
PERFORMANCE OBJECTIVES: COMBO Stent

- Short term:
  - Rapid Endothelial Coverage, allowing shorter DAPT
- Mid term:
  - Control of Neointimal Proliferation
    - Low rates of Restenosis and Target Lesion Revascularization, comparable to contemporary DES
- Long term:
  - Stable healing, durable results
    - Stable TLR rate over Time
    - No/Low rate of Late Stent Thrombosis
    - Reduced late neoatherosclerosis

Scanning Electron Microscopy at 28 days in an Atherosclerotic Rabbit Model



Distribution of uncovered struts (by each strut) as assessed by SEM



Lines represent median values, upper bars represent median plus 75th percentile, and lower bars represent median minus 25th percentile.

% Endothelial coverage by SEM

Endothelial coverage (%)	Combo (n=6)	Genous (n=6)	Xience Prime (n=6)	p value
Above struts	83.3 (34.1)	98.3 (20.6)	52.7 (48.0)	0.025
Between struts	93.3 (5.9)	87.5 (20.9)	92.0 (13.7)	0.714

Endothelial coverage at 28 days above struts by SEM was highest in Genous, followed by Combo, and lowest in Xience Prime. Endothelial coverage between struts was nearly identical.

REMEDEE
Combo Stent First-In-Man

JACC: CARDIOVASCULAR INTERVENTIONS
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The REMEDEE Trial

A Randomized Comparison of a Combination Sirolimus-Eluting Endothelial Progenitor Cell Capture Stent With a Paclitaxel-Eluting Stent

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Stephen G. Worthley, MBBS, PHD,‡ Sigmund Silber, MD, PHD,§
Stefan Verheye, MD, PHD,‖ Sandra Erbs, MD,¶ Mohd Ali Rosli, MD,#
Roberto Botelho, MD, PHD,** Ian Meredith, MBBS, PHD,†† Kui Hian Sim, MBBS,‡‡
Pieter R. Stella, MD, PHD,§§ Huay-Cheem Tan, MBBS, ‖‖ Robert Whitbourn, MBBS,¶¶
Sukumaran Thambar, MBBS,## Alexandre Abizaid, MD, PHD,*** Tian Hai Koh, MBBS,†††
Peter Den Heijer, MD, PHD,‡‡‡ Helen Parise, ScD,§§§ Ecaterina Cristea, MD,§§§
Akiko Maehara, MD,§§§ Roxana Mehran, MD§§§

Neuss, Munich, and Leipzig, Germany; Hong Kong, Hong Kong; Adelaide, Melbourne, and Newcastle, Australia; Antwerp, Belgium; Kuala Lumpur and Sarawak, Malaysia; Minas Gerais and São Paulo, Brazil; Utrecht and Breda, the Netherlands; Singapore, Singapore; and New York, New York

- 183 pts
- 2:1 RCT Combo vs. Taxus Liberte
- 1º endpoint: non-inf 9 mos LLL met

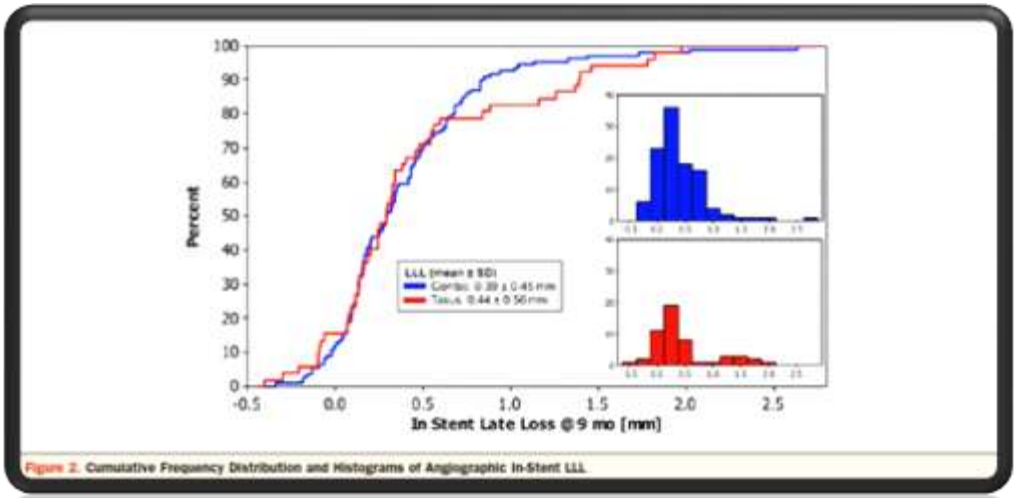


Figure 2. Cumulative Frequency Distribution and Histograms of Angiographic In-Stent LLL

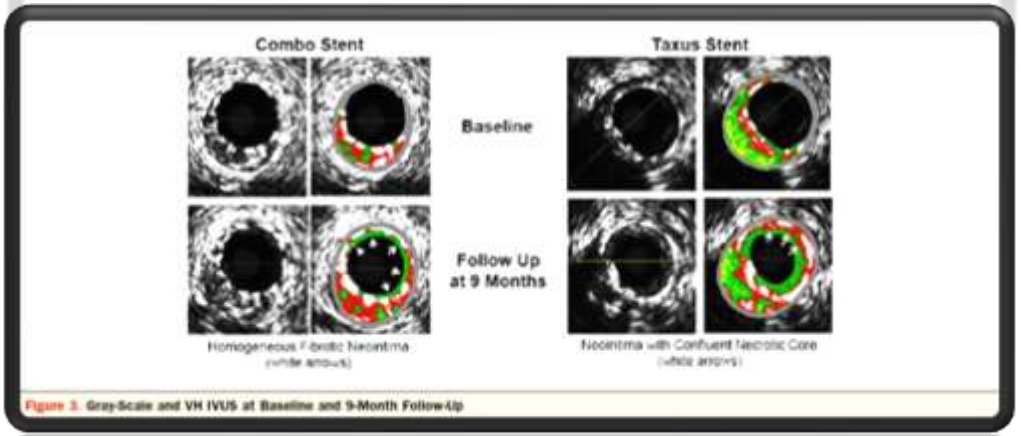
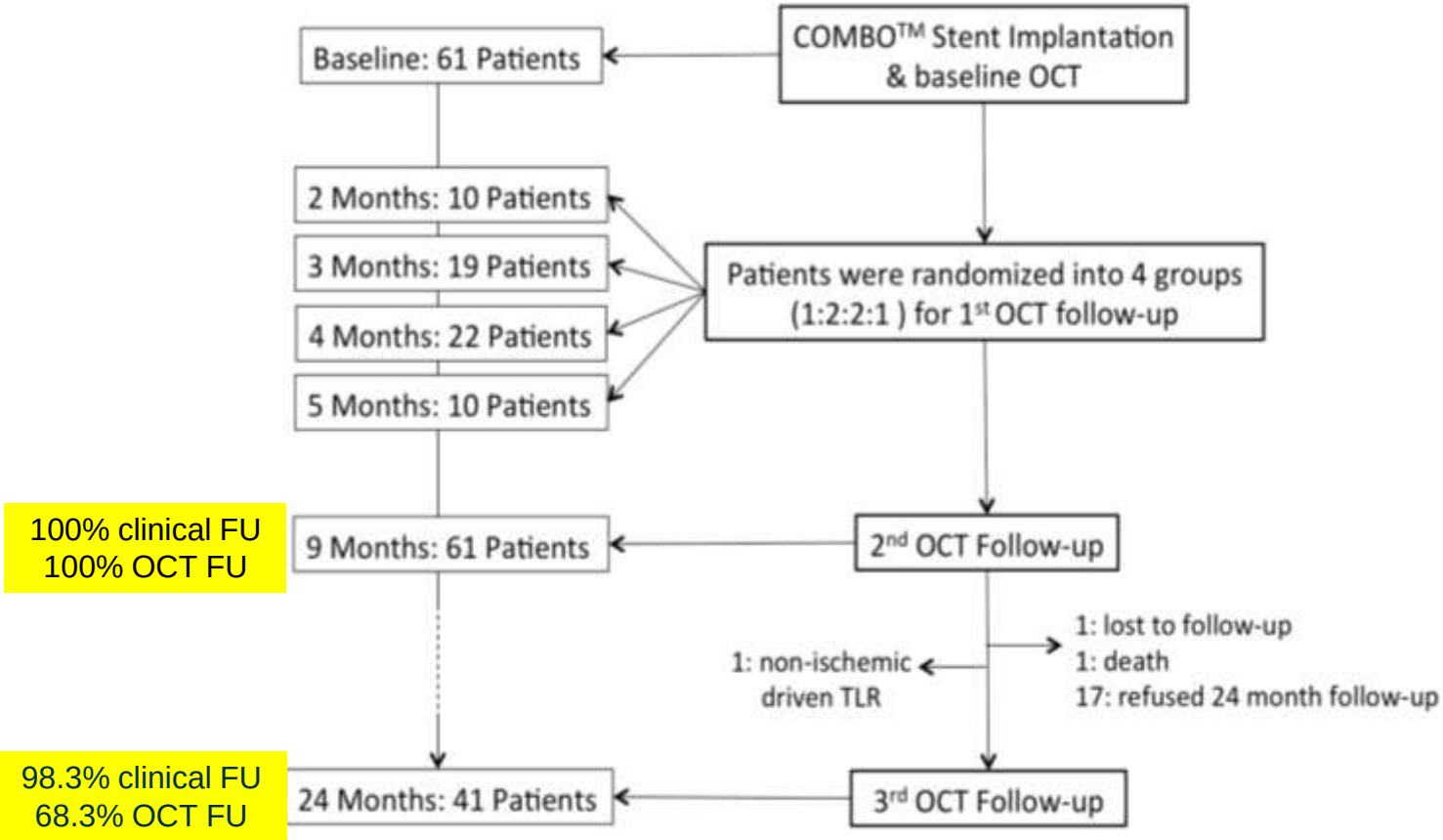


Figure 3. Gray-Scale and VH IVUS at Baseline and 9-Month Follow-Up

EGO COMBO

Trial Study Design

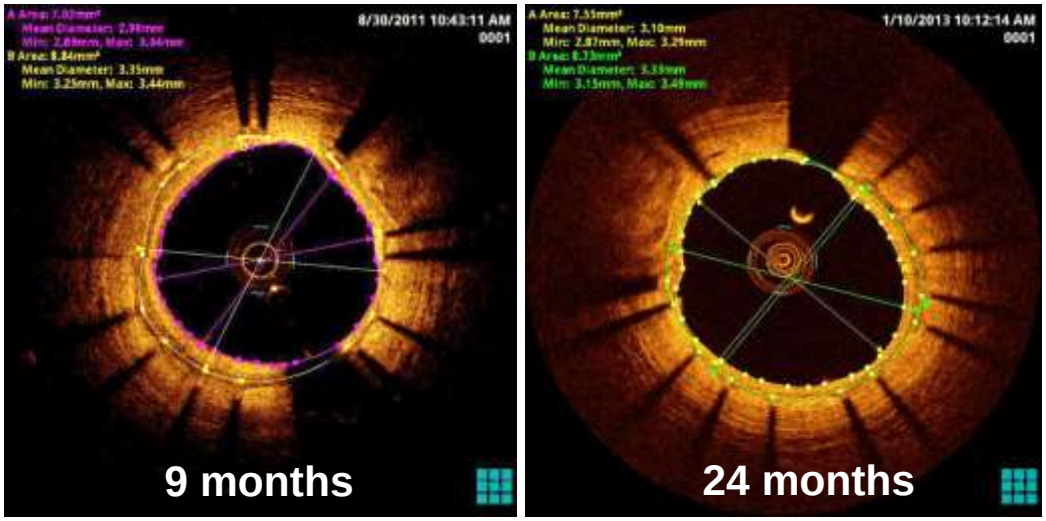
Patient randomization and OCT follow-up



S Lee, TCT 2014

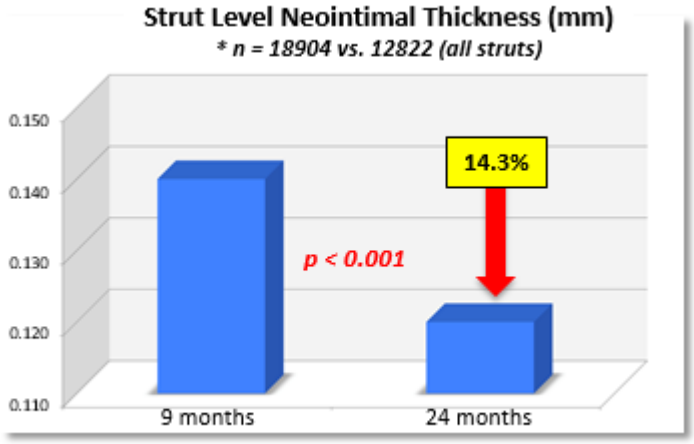
EGO COMBO

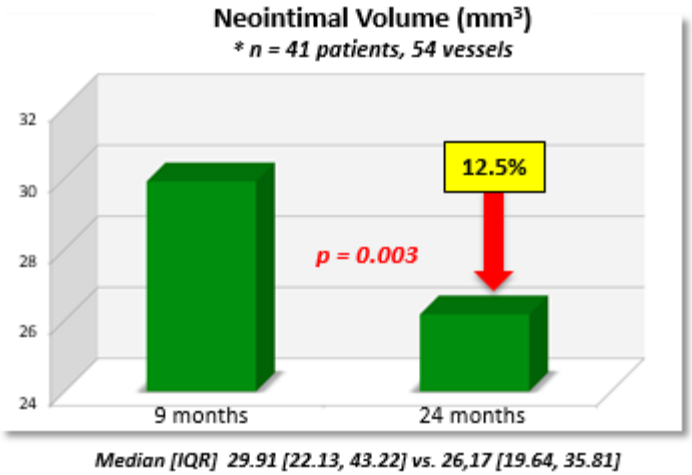
OCT documented neo-intimal regression from 9 to 24 month



<u>Increased</u> Lumen Area and <u>decreased</u> Neointimal Area from 9 to 24 months

- Results are consistent with NI maturation and organization
- No neoatherosclerosis





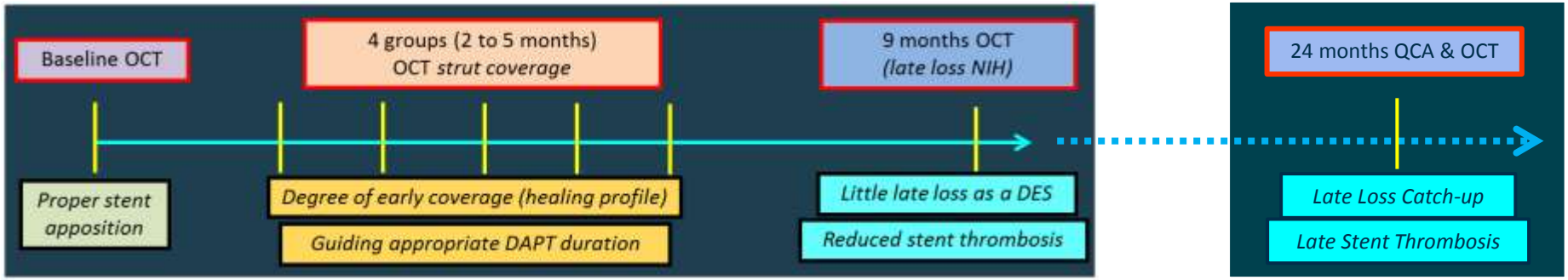
Median [IQR] 29.91 [22.13, 43.22] vs. 26,17 [19.64, 35.81]

Mount Sinai Heart

S Lee, TCT 2014

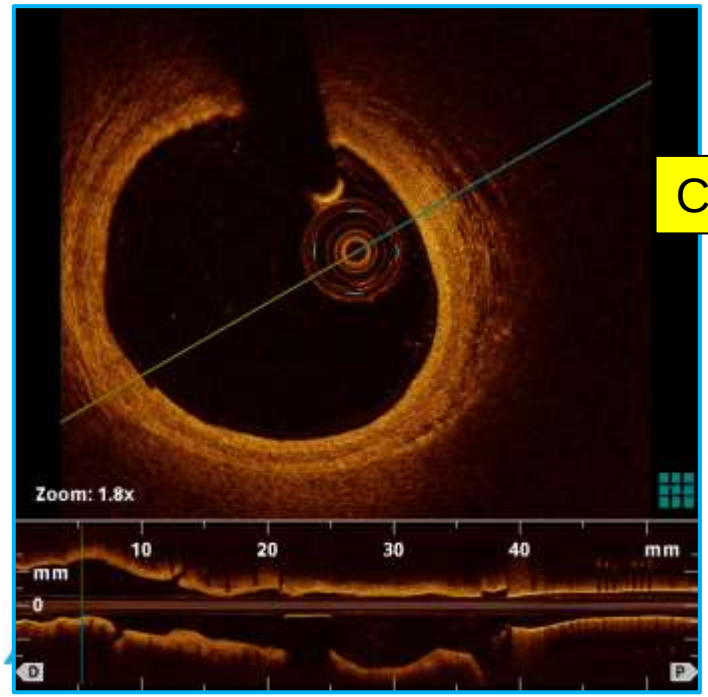
21st CardioVascular Summit TCTAP 2016

EGO-COMBO Study Design *(Longitudinal Sequential OCT FUs 0-24M)*



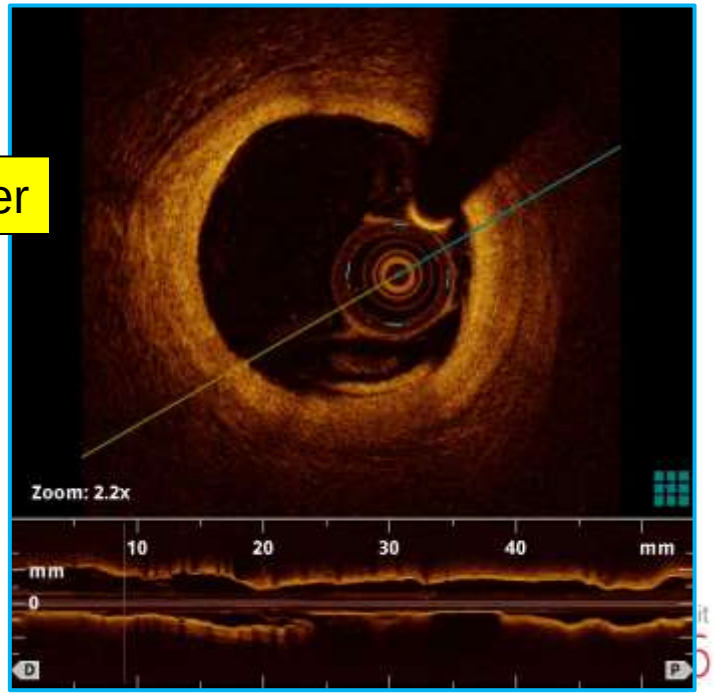
With core lab. adjudication, the dual therapy COMBO Stent is the first DES ever with a healing profile established, and appears to be a novel DES with durable outcomes.

Abluminal sirolimus drug coating	***Luminal antibody coating***
• Optimal neointimal suppression	• Excellent healing without neo-atherosclerosis
• Low neointimal thickness	• Plaque regression rather than progression
• Low neointimal volume	• No sun-flowering or late positive remodeling
• Low in-stent % plaque volume	• No even a single micro-thrombus detected
• ***Durable patent artery without ISR***	• ***Stable pro-healing benefits***



Combo

Cypher



Same patient
2 lesions on LAD
24M Combo Proximal
22M Cypher Distal

Initial Combo Clinical Experience

Shedding light on three aspects of healing:

- **EARLY: Strut "coverage"** — *REMEDEE*[*], *EGO COMBO*[**], *REMEDEE OCT*[***]
  - OCT @ 2 - 9 months
- **MID TERM: Restenosis** — *REMEDEE*[*], *EGO COMBO*[**], *REMEDEE OCT*[***]
  - NI formation & Late Loss
    - OCT @ 2 - 9 months
  - QCA @ 9 months
  - NI Characterization @ 9 months
    - OCT: Low Intensity Tissue & Micro Vessels in NI
    - IVUS-VH: Necrotic Core in NI
- **LONG TERM: Biostability** — *REMEDEE*[****], *EGO COMBO*[**], *REMEDEE OCT*[***]
  - Clinical FU out to 48 months — *REMEDEE Registry*[*****]
  - OCT FU out to 24 months

[*] M. Haude, **EuroPCR 2012**
[**] **S. Lee, TCTAP 2014**
[***] **U. Landmesser, TCT 2012**
[****] R. Mehran, EuroPCR 2015
[*****] R. de Winter, TCT 2015

One Year Results of the REMEDEE Registry

Clinical Outcomes After Deployment of the Abluminal Sirolimus-Coated Bioengineered Stent (COMBO) in a Multicenter, Prospective Postmarket Registry

Robbert J de Winter, MD PhD FESC

On behalf of the REMEDEE Registry Investigators

Lesion Characteristics

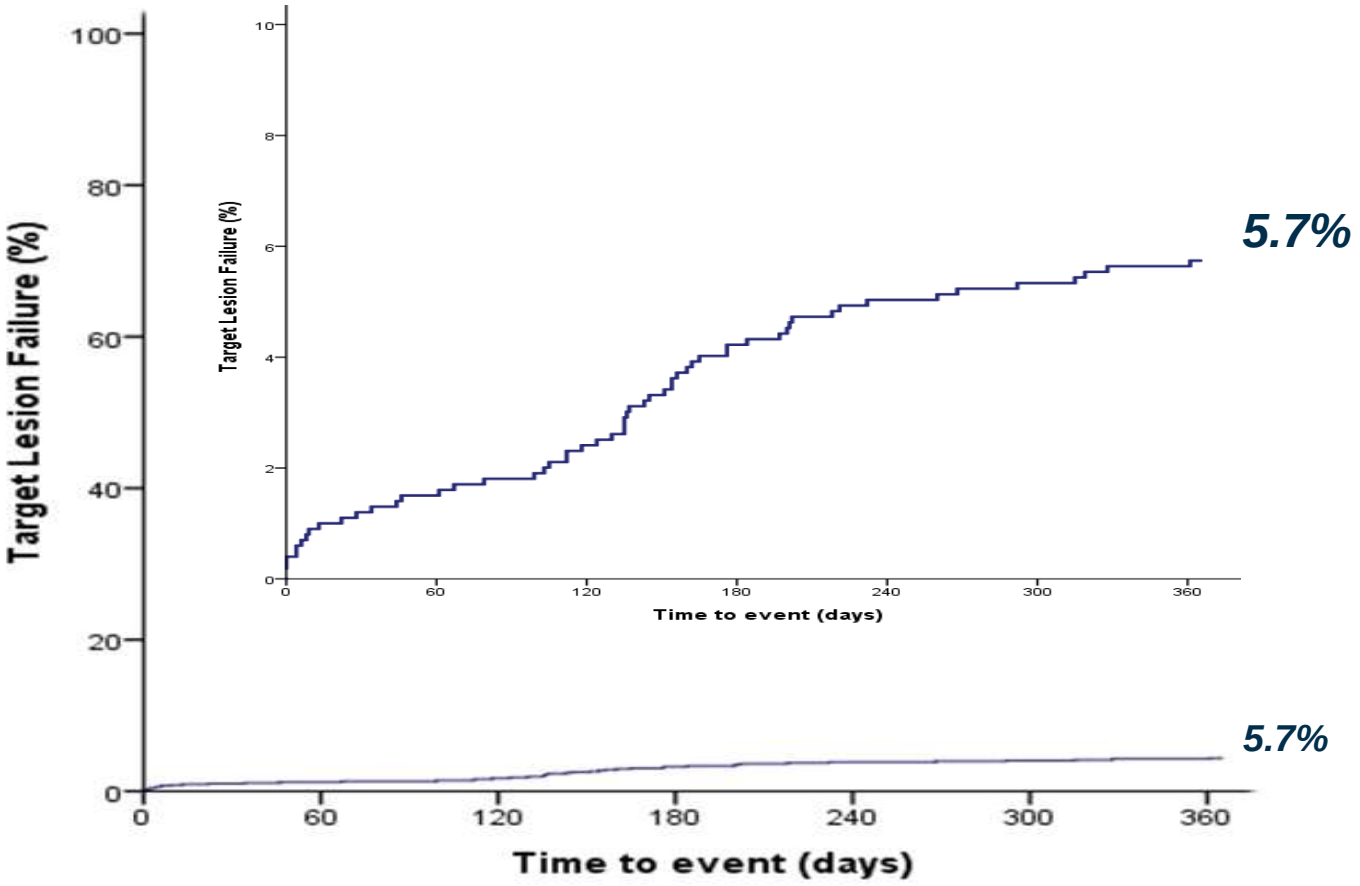
Multivessel disease (>1 vessel, >70%)	**21.1%**
Treated lesions (n=1511)	
Left main	**1.3%**
LAD	**50.6%**
LCx	**20.2%**
RCA	**26.1%**
Bypass graft	**1.8%**
Number of vessels treated	
One vessel PCI	**89.5%**
Multivessel PCI	**10.5%**

AHA/ACC lesion type	
A	**16.4%**
B1	**24.9%**
B2	**37.5%**
C	**21.1%**

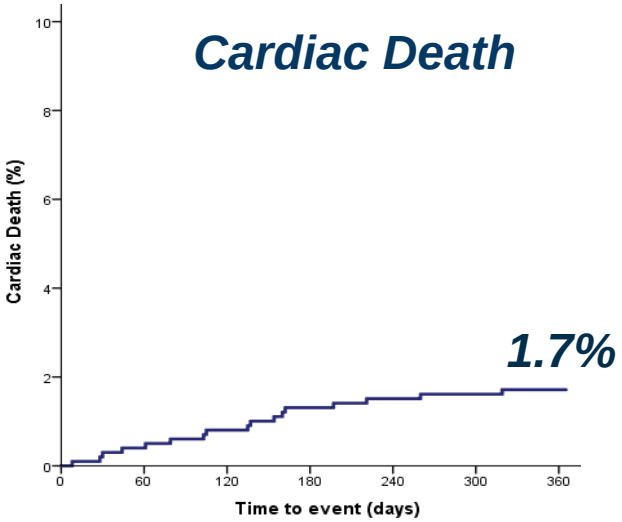
} 50%

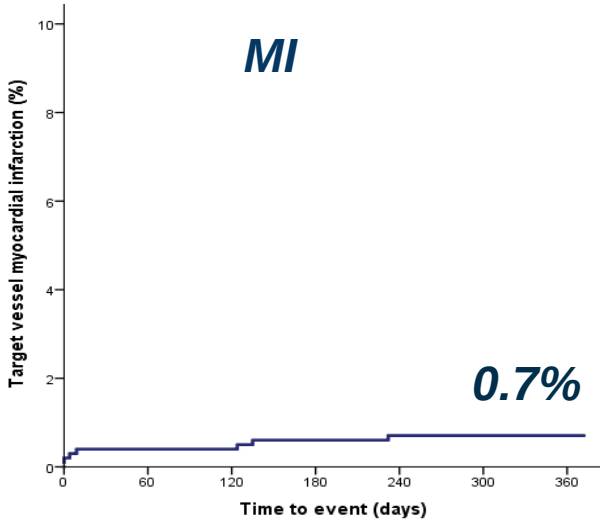
TIMI flow pre-procedure	
0	**14.5%**
1	**4.5%**
2	**9.8%**
3	**71.3%**

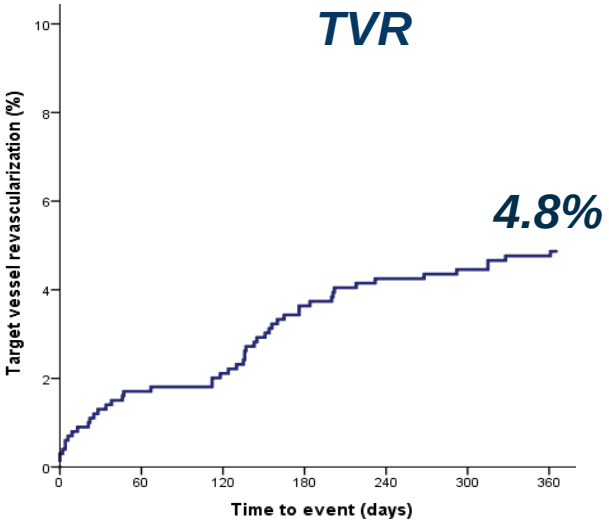
Primary endpoint: Target Lesion Failure

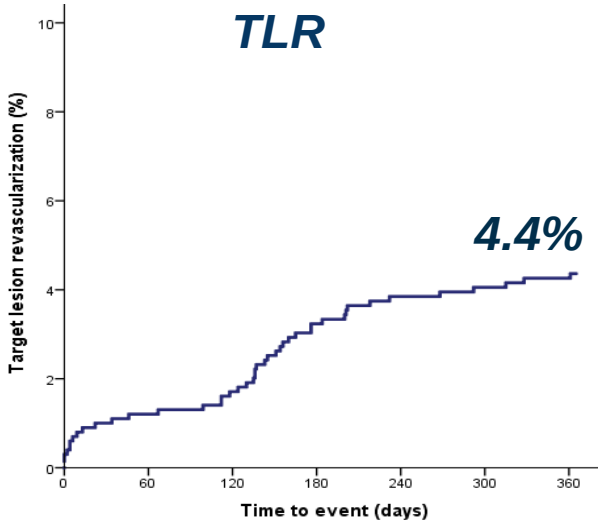


Secondary endpoints

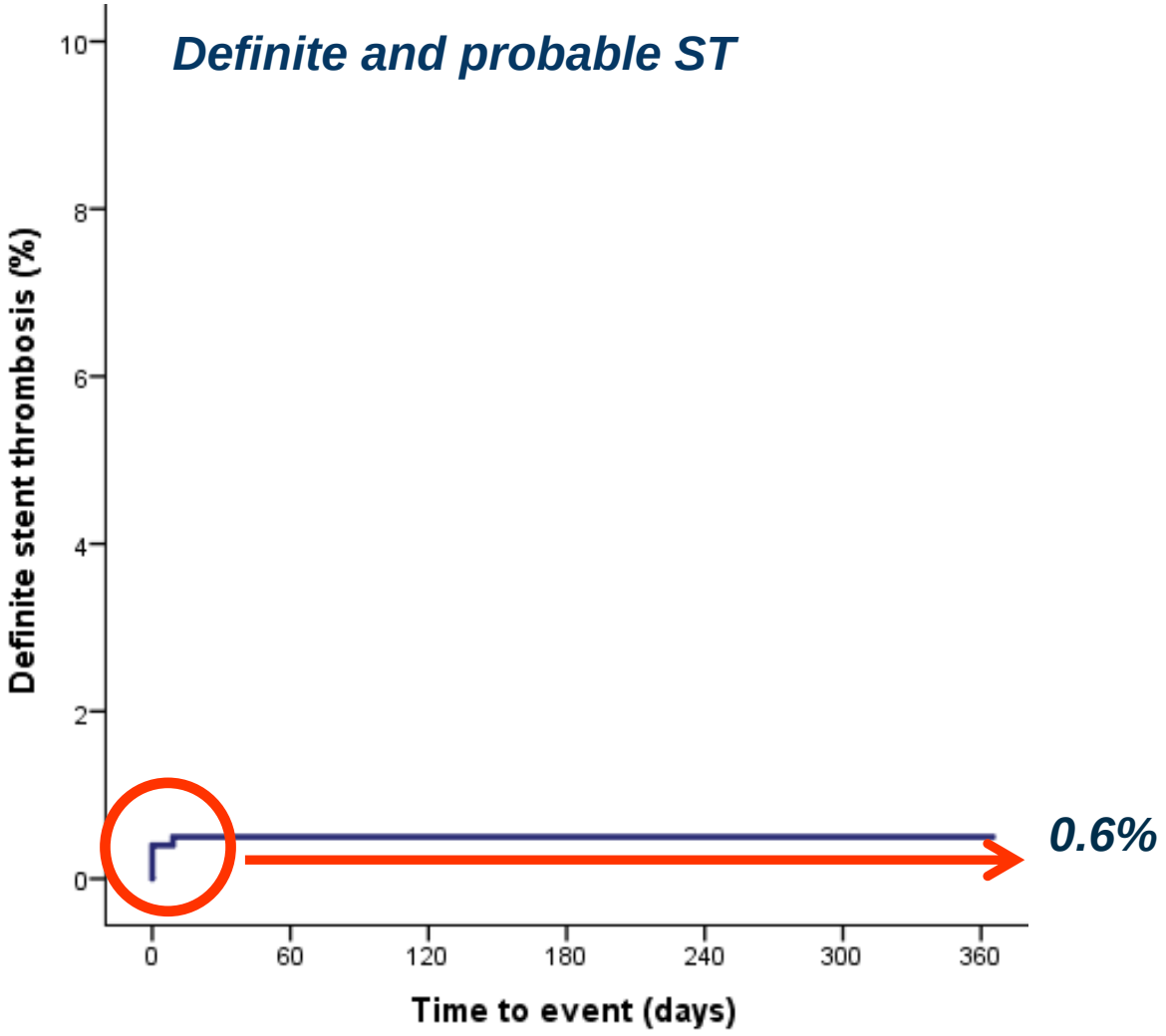






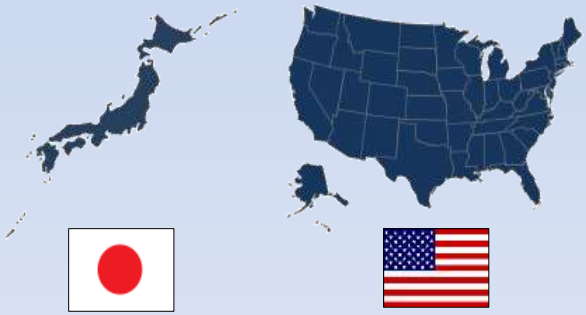


Stent thrombosis



HARMONEE

Harmonized **A**ssessment by **R**andomized, **M**ulti-center Study of **O**rbus**NE**ich's COMBO St**E**nt



HARMONEE Study Organization

***Sponsor*:**

- OrbusNeich Medical

***Global PIs*:**

- Dr. Shigeru Saito
- Dr. Mitchell Krucoff

***National Coordinators*:**

- *USA:* Dr. Roxana Mehran
- *Japan:* Dr. Shigeru Nakamura

Steering Committee Chair:

- Dr. David Kong

Site Management:

- *Japan*: CMIC
- *USA*: DCRI

***Clinical Event Adjudication*:**

- DCRI (Japan-USA)

***Data Safety Monitoring*:**

- DCRI (Japan-USA)

FFR Core Laboratory:

- UH, Case Western Reserve
  Dr. Hiram Bezerra, Director

***Angiographic Core Laboratory*:**

- CRF
  Dr. Philippe Genereux, Director

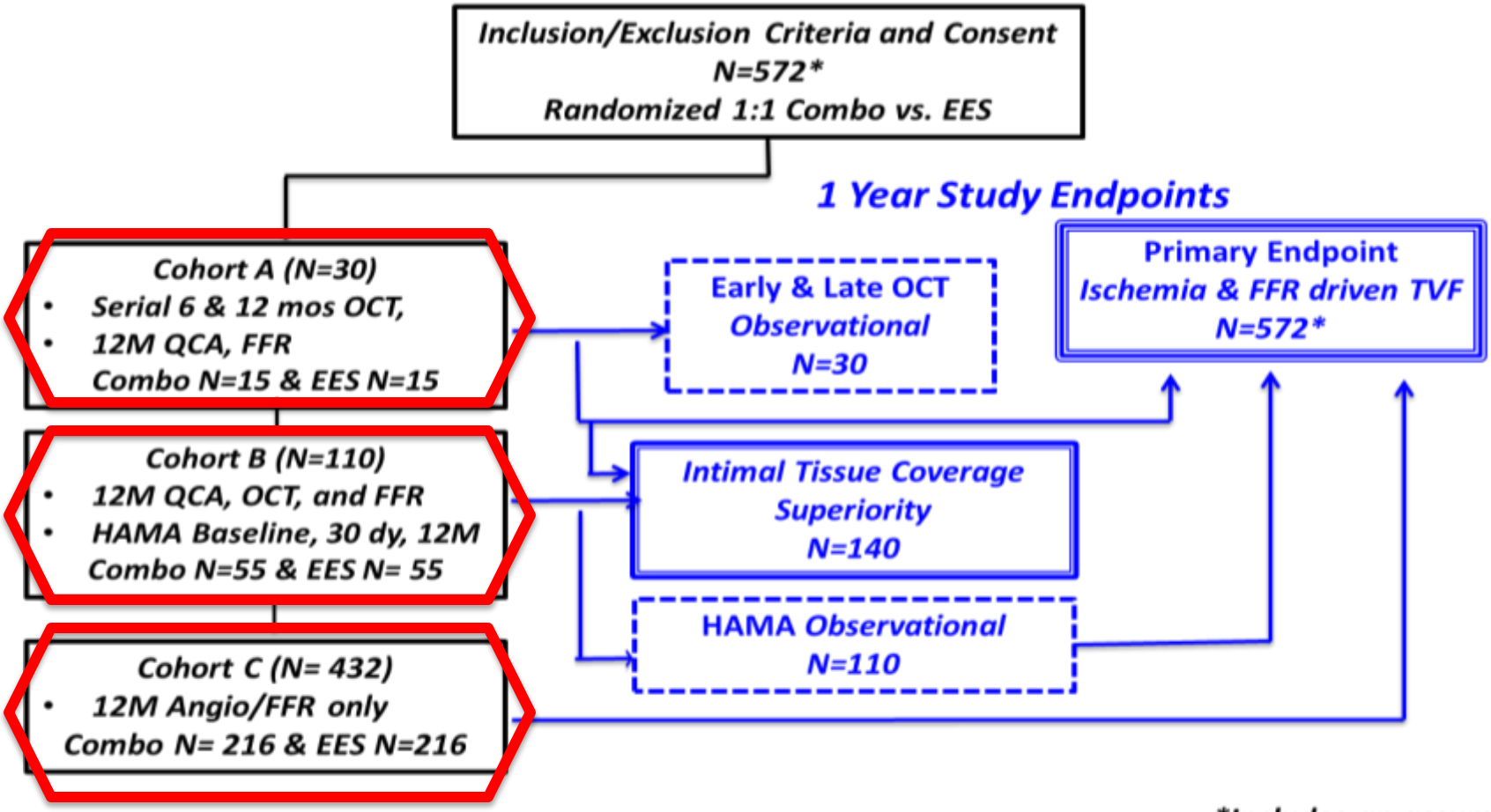
OCT Core Laboratory:

- CRF
  Dr. Akiko Maehara, Director

HAMA Core Laboratory:

- Celerion Switzerland AG

HARMONEE Study Design



*Includes an assumed 5% 1 yr lost to F/U

HARMONEE Study Endpoints

Primary endpoint (clinical effectiveness):

- Non-inferior TVF* at 1 year (including FFR) vs. state-of-the-art second-generation DES

- Superior TVF vs imputed BMS

*Clinically driven target vessel failure [TVF], defined as cardiac death, target-vessel MI, or ischemia-driven TVR by percutaneous or surgical methods.

HARMONEE Study Endpoints

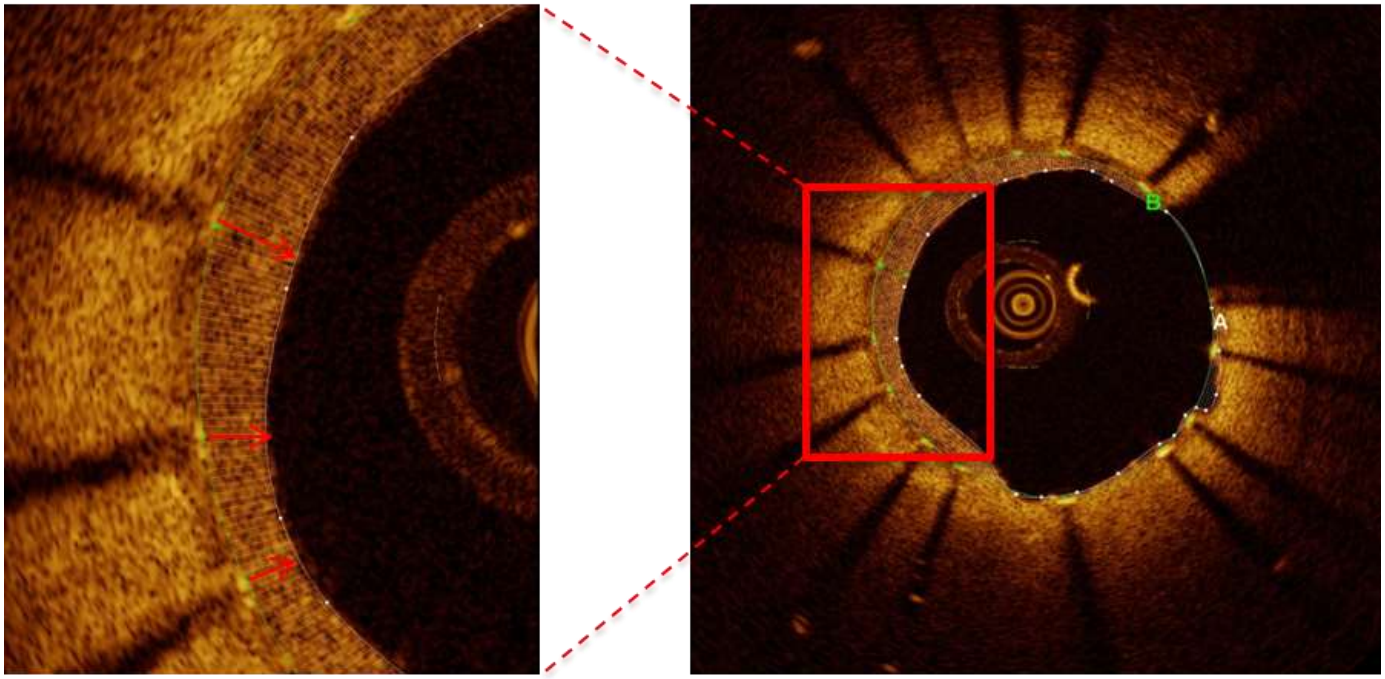
Secondary (mechanistic effectiveness)

Superior healthy level of intimal tissue strut coverage at 1 year vs. state-of-the-art second-generation DES quantified by OCT

Other Pre-Specified

- Death, myocardial infarction (MI), and stent thrombosis at 1 year
- Angiographic late lumen loss at 1 year vs. EES
- Safety of Combo:
  - Change in HAMA plasma levels at 30-day and 1-year follow-ups compared with baseline
  - OCT evaluation of intracoronary thrombosis and stent malapposition at 1 year
- Serial observation of both Combo and EES at 6 and 12 months in the same patients

OCT Measurement: 1 year healthy endothelium
EPC Mechanistic Surrogate



- Independent, Blinded Core Laboratory (CRF)
- Per strut, per frame, and per patient analysis
- Combo superiority to EES

Leaving “occulo-stenotic” PCI Behind

Fractional Flow Reserve (FFR):

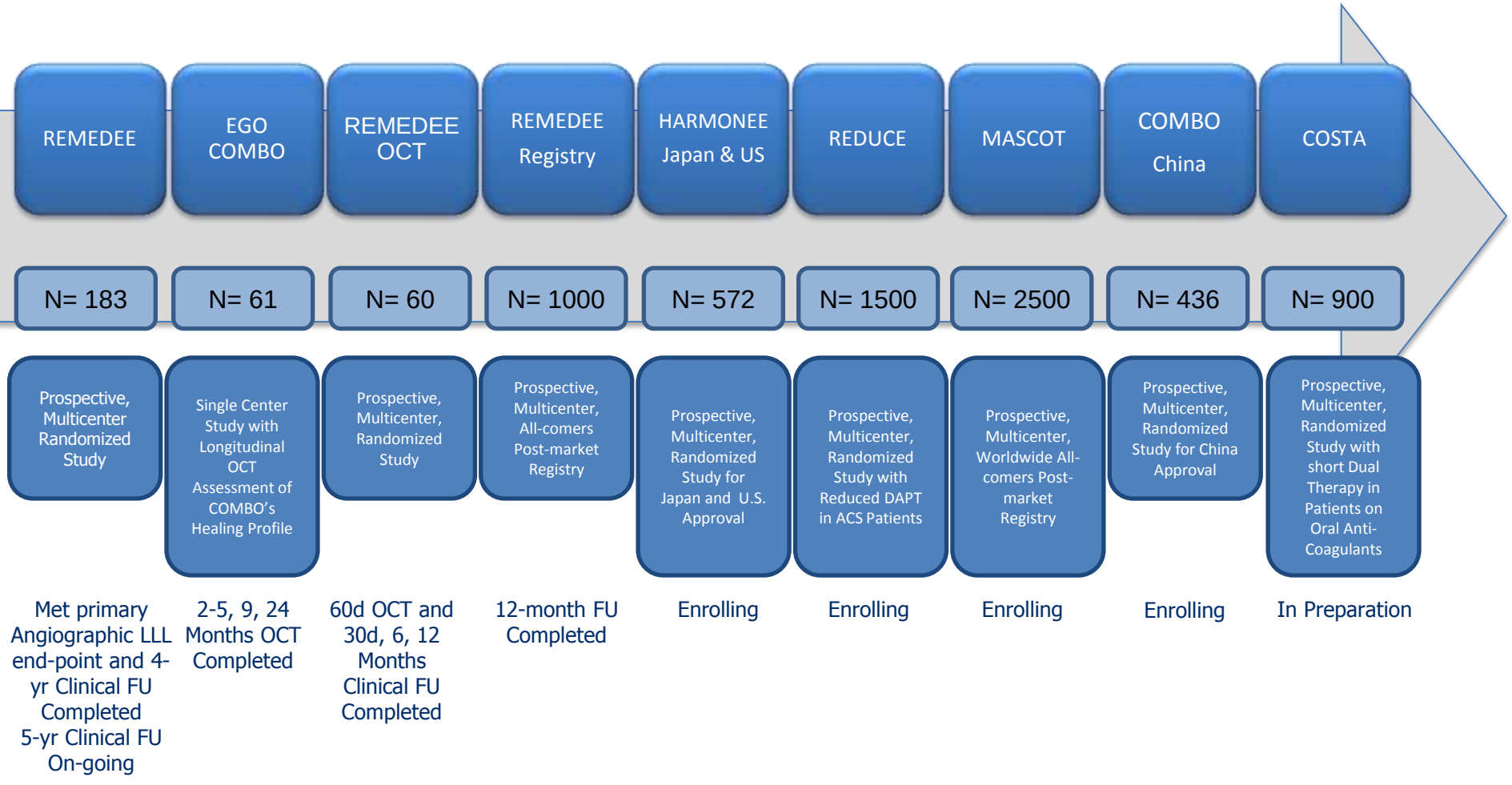
- All patients at 1 year
- All “re-looks”
- Core Lab quality assurance

Japan-USA HARMONEE Study

- First 4-component DES
- First biologic EPC capture technology
- First Japan-USA pivotal coronary DES study
- First physiologic & anatomic DES evaluation
- First “non-occulo-stenotic reflex” invasive F/U study

Enrolled 544***/572 patients!***

Combo Stent
Clinical Trial Program



Combo Stent Conclusions

- DES technology still evolving: Focus on “Active Healing”
- *EPC capture technology*: Novel “4th component” to enhance speed and completeness of endothelial healing
- Combo stent has been shown to be effective in the control of neointimal proliferation
  - Low clinical event rates out to 4 years
  - Mechanistic clinical studies have demonstrated a unique the ”healing profile”

Combo Stent Conclusions

- Japan-USA HARMONEE Study: On-going trial assesses clinical and mechanistic outcomes of Combo vs. EES
  - *TVF 1 year*
  - *OCT 6 months & 1 year*
  - *FFR: for all repeat revascularization*
- Large-scale Registries: “Real-world” experience
  - REMEDEE Registry at 12-mo FU (n=1000)
  - MACOT Registry enrollment complete (n=2500)
- Benefit of Combo stent technology in High Risk RCTs
  - REDUCE: Reduced DAPT in ACS Patients; 3-mo versus 12-mo
  - COSTA: short Dual Therapy in Patients on Oral Anti-Coagulants
- An ongoing comprehensive clinical trial program with 7000+ patient pool designed to validate the clinical performance of Combo

Thank You