Combo - A Combination Sirolimus Eluting Anti-CD34 Antibody Coated Stent: Technology, Development & Clinical Data

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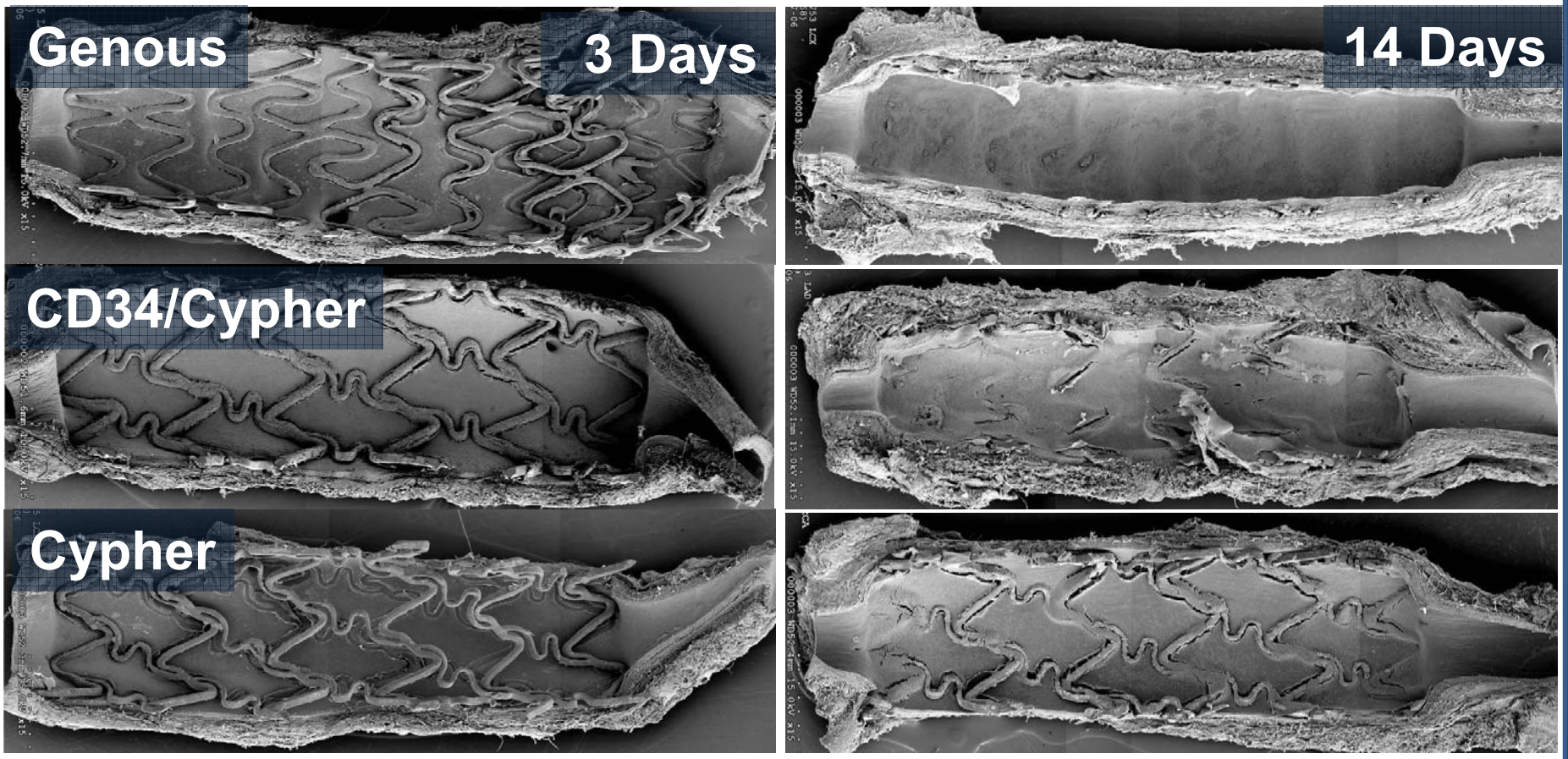
Conflict of Interest Disclosure

I am an employee of OrbusNeich Medical, Inc.

Addressing Unmet Needs with Contemporary PCI

- **Improve efficacy profile – stable outcomes over time**
  - **Limit neo-intimal proliferation**
  - **No chronic inflammation**
  - **Vessel healing**
- **Improve safety profile – eliminate late stent thrombosis**
  - **Rapid endothelial coverage and function**
- **Reduce dependency on DAPT**
  - **Avoids risk associated with DAPT discontinuation**
  - **Lowers bleeding risk and its complications**

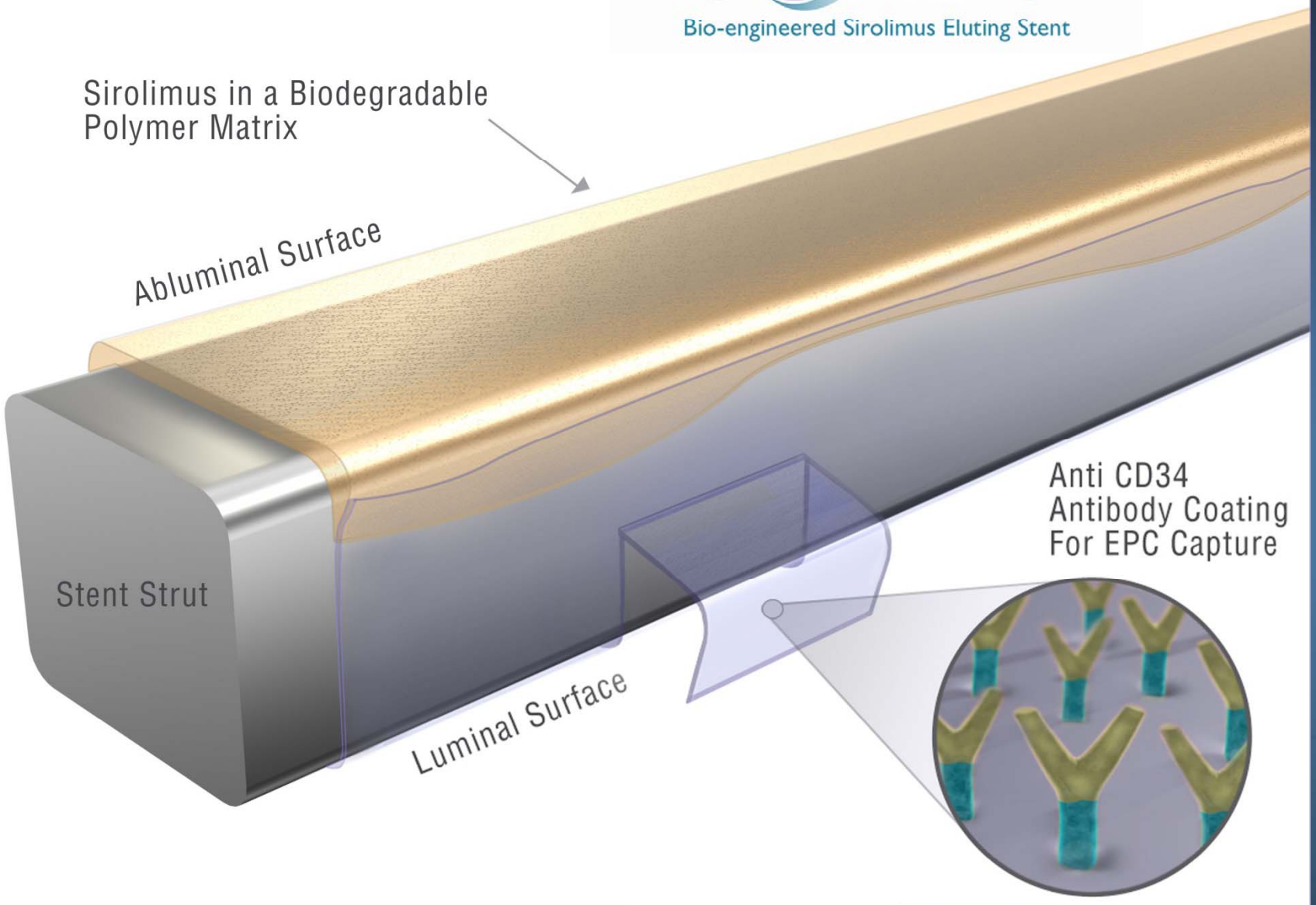
Stent Surface Coverage by SEM in Stented Porcine Coronary Arteries



Nakazawa G et al., JACC Cardiovasc Interv. 2010 Jan;3(1):68-75.

Combo Dual Therapy Stent

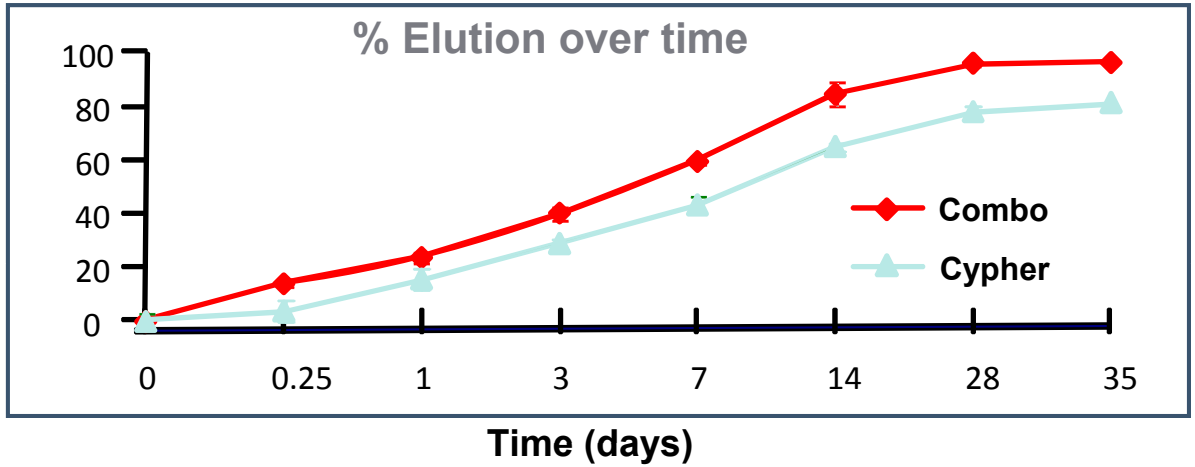
COMBO™
Bio-engineered Sirolimus Eluting Stent



Granada et al., Circ Cardiovasc Intervent. 2010; 3:257-266

Abluminal Sirolimus Drug Delivery

from a completely biodegradable polymer matrix

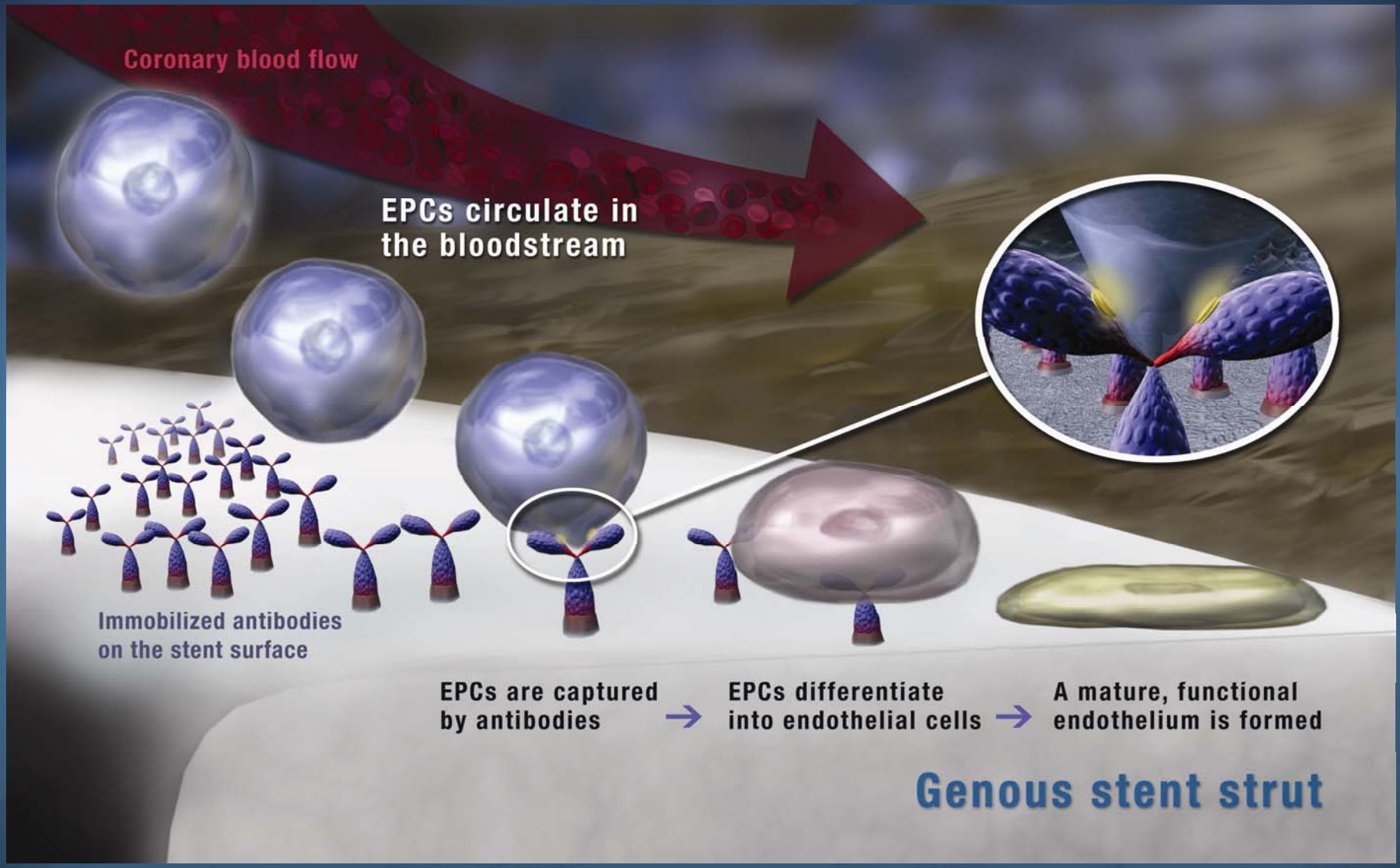


In vivo **elution profile of Combo and Cypher (% of total drug eluted over time)**

Full and complete polymer matrix degradation within 90 days

Granada et al., Circ Cardiovasc Intervent. 2010; 3:257-266

Endothelial Progenitor Cell (EPC) Capture



The REMEDEE Study: A Randomized Comparison of a Combination Sirolimus Eluting EPC Capture Stent with a Paclitaxel Eluting Stent

Michael Haude, MD

On behalf of the REMEDEE Investigators

TCT 2011 Late Breaking Clinical Trial

November 11, 2011

REMEDEE Study Design

Objective:

- To demonstrate non-inferiority of the Combo Stent compared to the TAXUS Liberté ® stent for the primary endpoint of 9-month angiographic in-stent late lumen loss

Major Inclusion Criteria:

- Single de-novo lesions in native coronary arteries
- Lesion length ≤ 20 mm
- 2.5 mm to 3.5 mm in diameter

Major Exclusion Criteria:

- Acute Myocardial Infarction
- Ostial lesions
- Unprotected left main with ≥ 50% stenosis

REMEDEE Trial Summation

- FIM 2:1 randomized study
  - 124 Combo & 59 Taxus patients enrolled at 17 sites
- Study endpoints
  - Primary – non-inferiority of angiographic 9 month in stent late loss
  - Secondary – stent thrombosis and clinical endpoints out to 5 years; IVUS follow-up subset
- Balanced patient populations with significant co-morbidities
- No significant differences in baseline lesion characteristics

Angiographic In-Stent Late Lumen Loss
Statistical Analysis

	Combo (N=124)	**TAXUS** (N=59)	**Margin of Non-Inf, Δ** (mm)	**Non-inferiority p-value**	**Difference** [95% CI]	**Superiority p-value**
In-stent Late Lumen Loss at 9 months (mm)						
N	109	52				
mean ± SD	0.39 ± 0.45	0.44 ± 0.56	0.2	0.0012	-0.05 [-0.21,0.11]	0.5514
(min, max)	(-0.34, 2.63)	(-0.40, 1.97)			N/A	N/A

Full analysis set: ITT patients with qualifying 9-month angiographic follow-up included in the analyses.

Late loss estimated by Angiographic Core Lab for patients with available 9-month qualifying angiogram.

9-Month Binary Angiographic Restenosis and In-Segment Late Loss

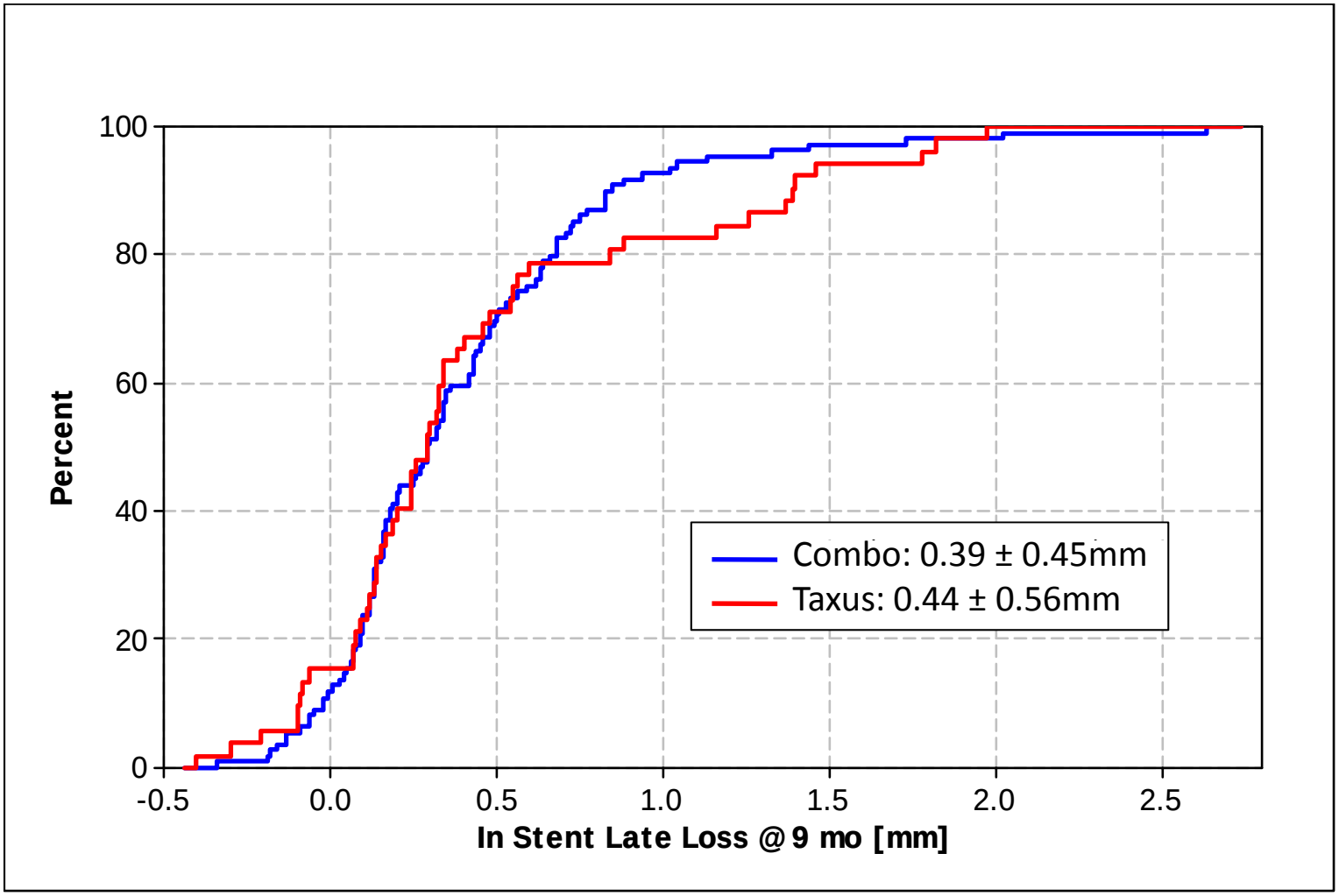
	Combo (N=124)	**TAXUS** (N=59)	**p-value**
Restenosis (%)			
In-stent	5.5%	9.6%	0.34
In-segment	8.3%	13.5%	0.30
Minimum Lumen Diameter (MLD) (mm)			
In-stent, mean ± SD	2.31 ± 0.58	2.30 ± 0.56	0.86
In-segment, mean ± SD	2.09 ± 0.56	1.97 ± 0.57	0.19
In-stent late lumen loss (mm)			
mean ± SD	0.39 ± 0.45	0.44 ± 0.56	0.55
In-segment late lumen loss (mm)			
mean ± SD	0.27±0.46	0.41±0.54	0.08
Proximal In-segment, mean ± SD	0.19 ± 0.44	0.29 ± 0.53	0.24
Distal In-Segment, mean ± SD	0.09 ± 0.30	0.13 ± 0.30	0.45

Conclusions

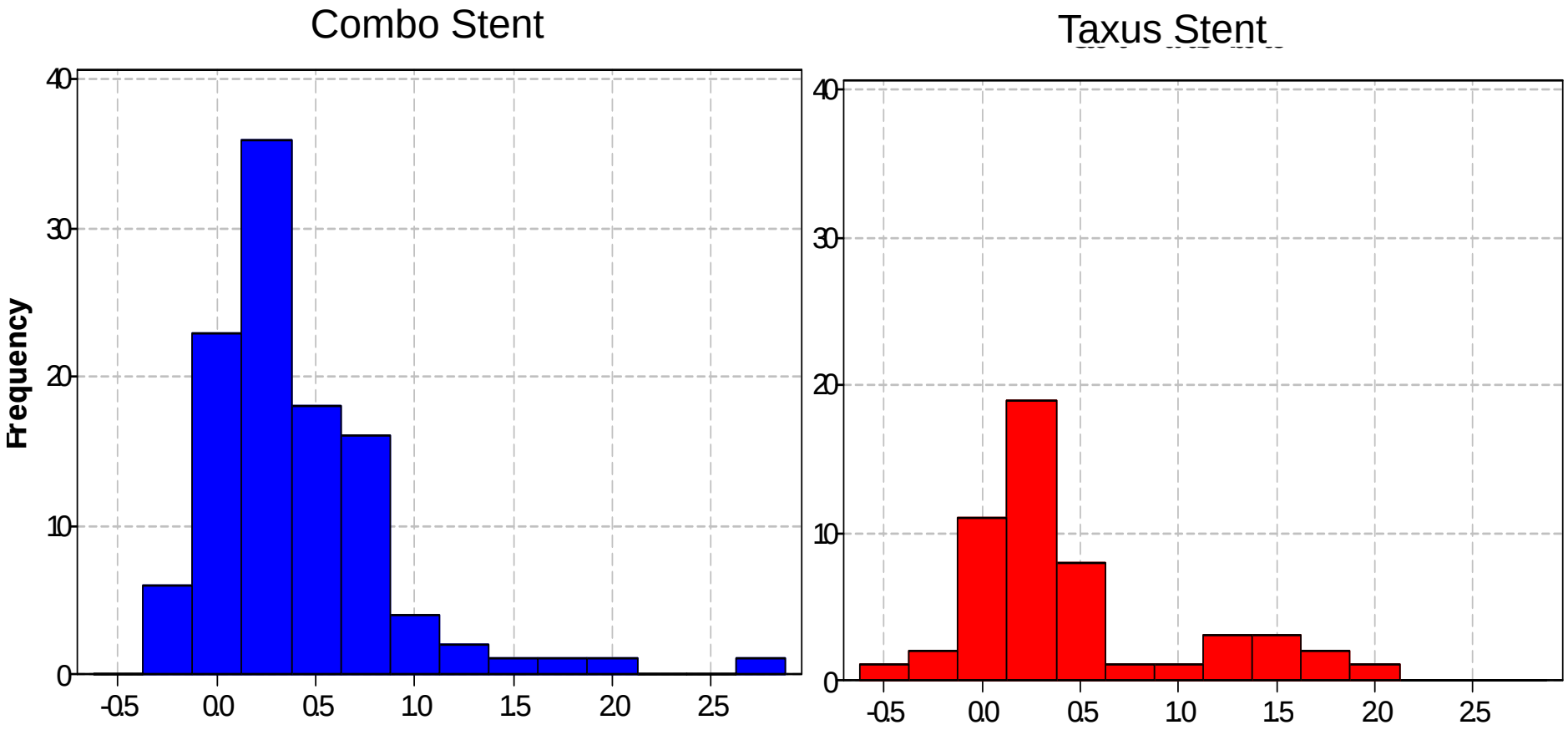
In this First-In-Man study, the COMBO Dual Therapy Stent effectively controls neointimal proliferation:

- **0.39 mm average angiographic in-stent late loss at 9 months with the Combo stent is non-inferior to the Taxus Liberté stent**
- **In-stent and In-segment Late Loss, and Binary Restenosis Rates are accordingly low and comparable to the Taxus Liberté stent**
- **Overall low rate of clinical events in both groups, including no stent thrombosis**
- **Combo shown to be effective & safe**

REMEDEE Cumulative Distribution of Angiographic In-stent Late Loss at 9 Months



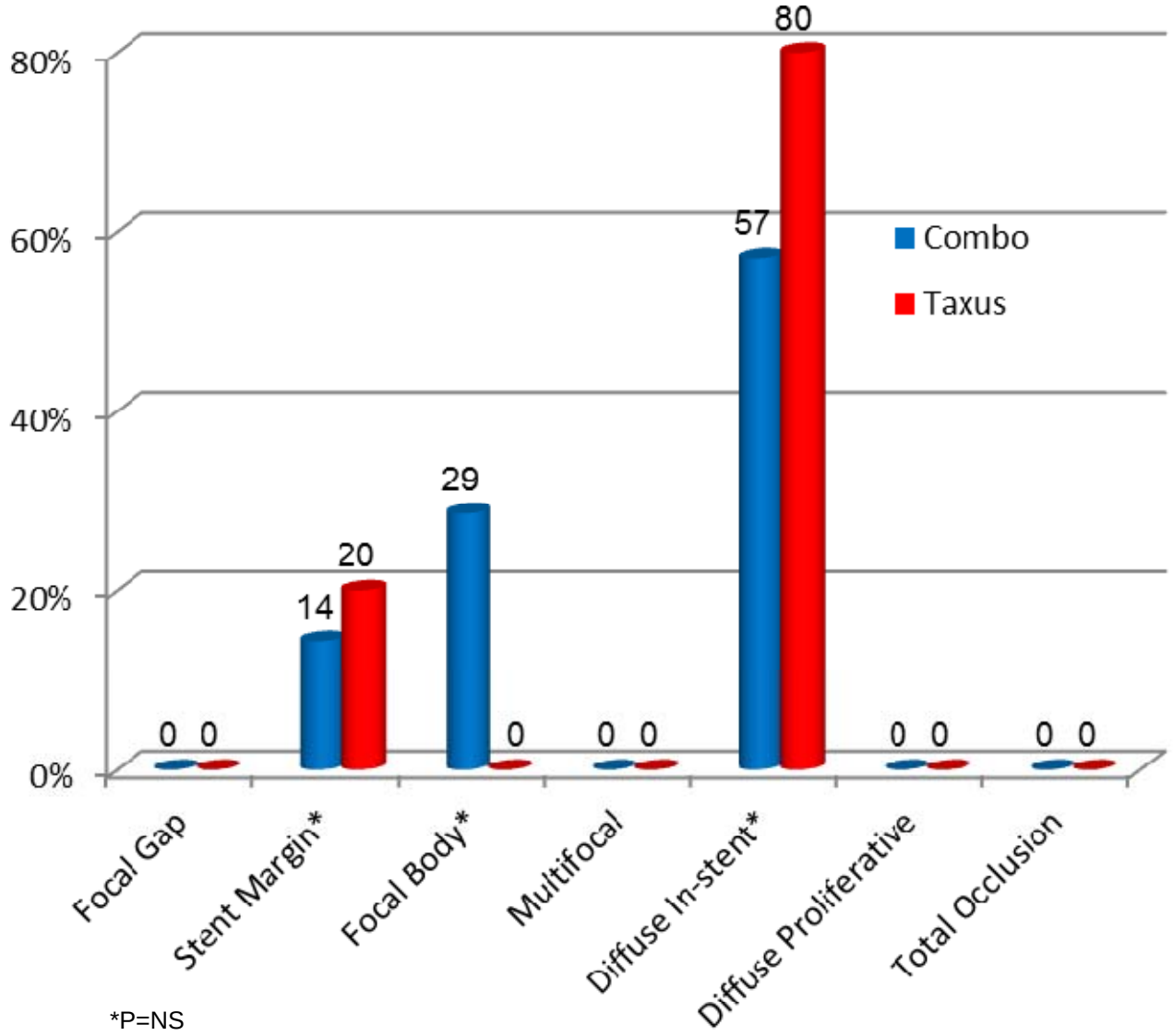
REMEDEE Histograms of In-stent Late Loss at 9 Months



LLL distributions show different patterns:

- Combo Stent: slight tail (n= 109)
- Taxus stent: bimodal appearance (n= 52)

REMEDEE Restenosis Pattern of Recurrence at 9 Months by QCA



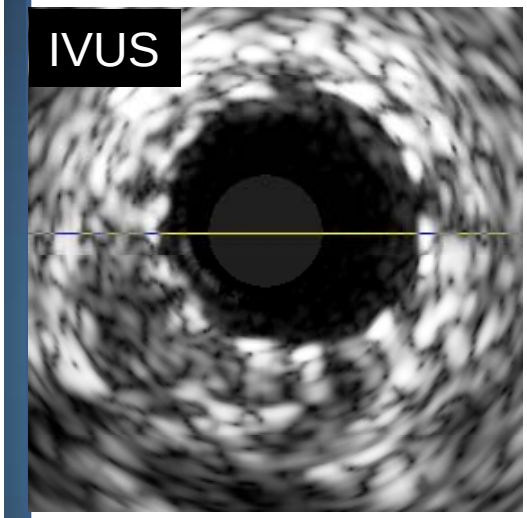
*P=NS

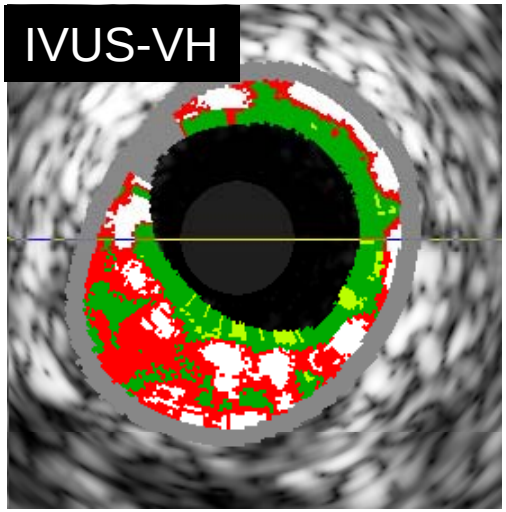
REMEDEE IVUS Endpoints at 9 Months

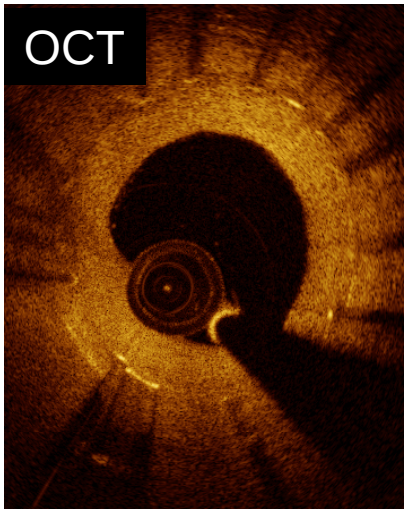
	Combo (N=35)	**TAXUS** (N=15)	**p-value**
Neointimal hyperplasia volume (mm^3)			
mean ± SD	21.53 ± 21.71	25.95 ± 18.65	0.50
Relative difference of NIH Volume	*(17% less NIH volume)*		
In-stent volume obstruction (%)			
mean ± SD	15.24 ± 14.22	14.59 ± 8.38	0.84

REMEDEE IVUS, IVUS-VH, and OCT at 9 Month F/U

Combo

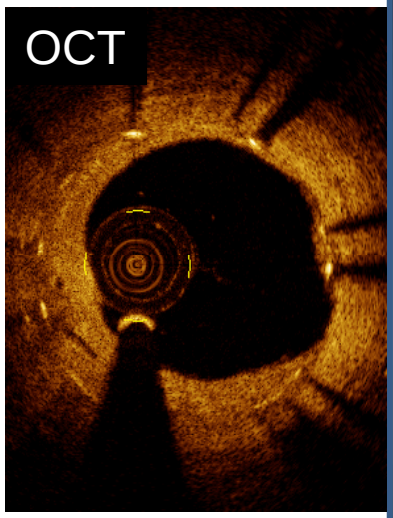






Homogenous tissue coverage of the stent strut

TAXUS



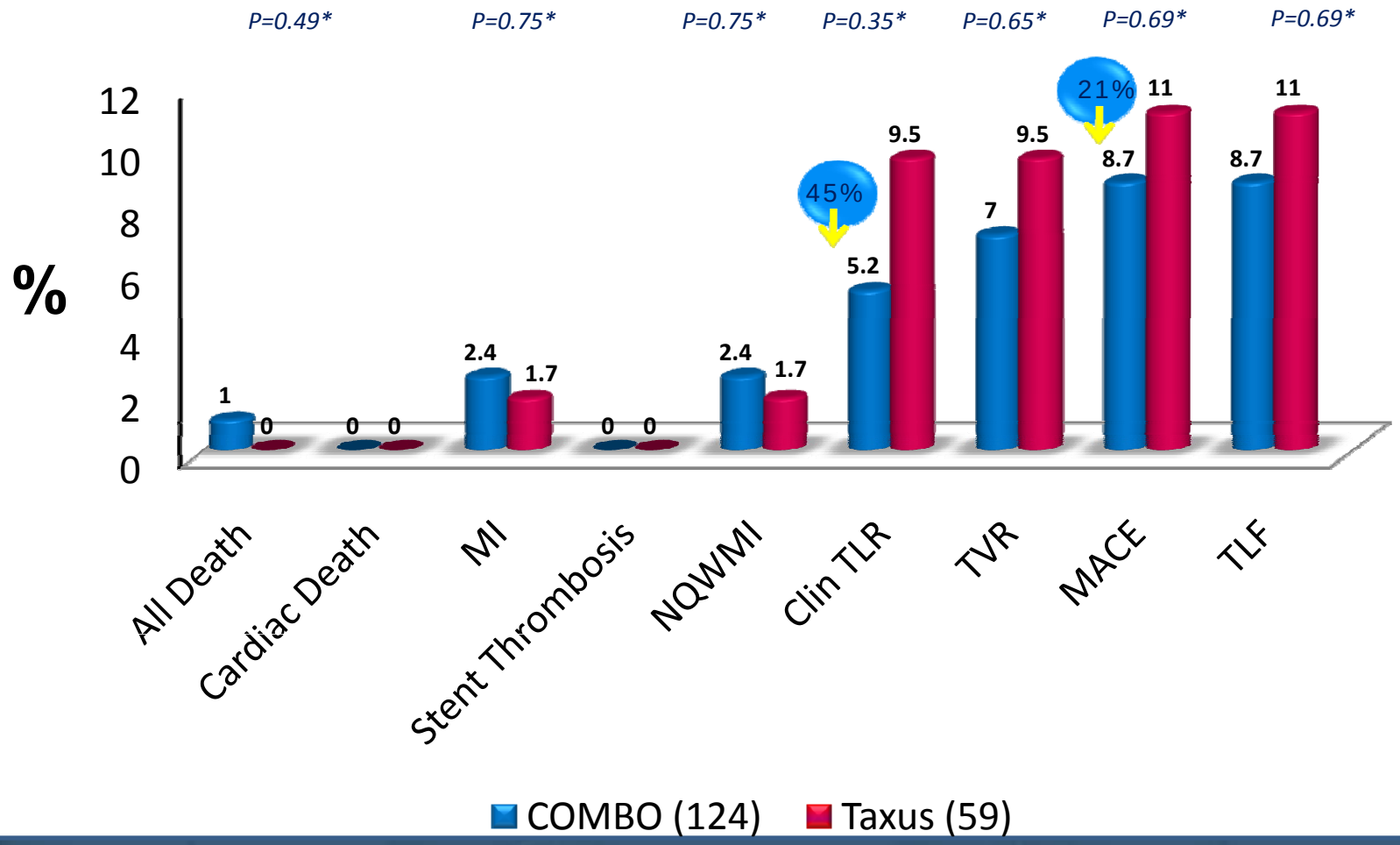
Heterogenous stent strut coverage

REMEDEE What's Different?
Presentation and Morphology of Restenosis

- **A divergence in the cumulative frequency distribution of late loss**
- **The patterns of late loss**
  - Combo relatively tightly distributed with a slight tail
  - Taxus more of a bimodal pattern
- **The patterns of restenosis**
  - Combo in-stent focal and diffuse
  - Taxus majority stent margin and diffuse
- **NI hyperplasia volume by IVUS** (17% reduction)
- **Difference in morphology by IVUS, VH-IVUS, and OCT**
  - Combo = homogeneous
  - Taxus = heterogeneous

These differences in presentation and morphology of restenosis corresponded with marked differences in clinical results . . .

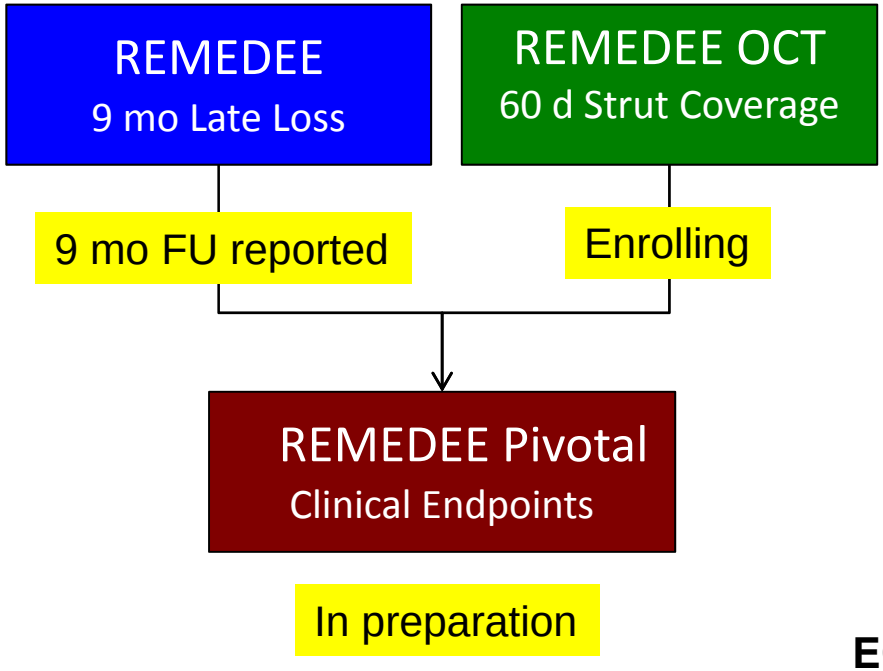
REMEDEE Clinical Results at 9 Months Follow Up



REMEDEE Clinical Trial Program

To demonstrate effectiveness in reduction of late loss:

- ✓ Combo : Taxus Liberte 120 : 60 patients
- ✓ stable patients;
- ✓ de-novo lesions
- ✓ Primary end point: late loss @ 9 mo
- ✓ non-inferiority design
- ✓ LPI: Aug 2010



To demonstrate rapid strut coverage:

- ✓ Combo : Xience V 30 : 30 patients
- ✓ ACS patients (STEMI & Non-STEMI)
- ✓ de-novo lesions
- ✓ Primary end point: strut coverage by OCT @ 60 days
- ✓ superiority design
- ✓ FPI: Oct 2011

EGO Combo:

- ✓ Serial OCT

Combo Dual Therapy Stent

- **Improve efficacy profile – stable outcomes over time**
  - Limit neo-intimal proliferation – sirolimus elution
  - No chronic inflammation – completely biodegradable polymer
  - Vessel healing – abluminal drug elution & luminal EPC capture
- **Improve safety profile – eliminate late stent thrombosis**
  - Rapid endothelial coverage and function – EPC capture
- **Reduce dependency on DAPT – vessel healing**
  - Avoids risk associated with DAPT discontinuation
  - Lowers bleeding risk and its complications