Coronary Stent Innovation: EPC Capture

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HBD East 2017 Think Tank Meeting
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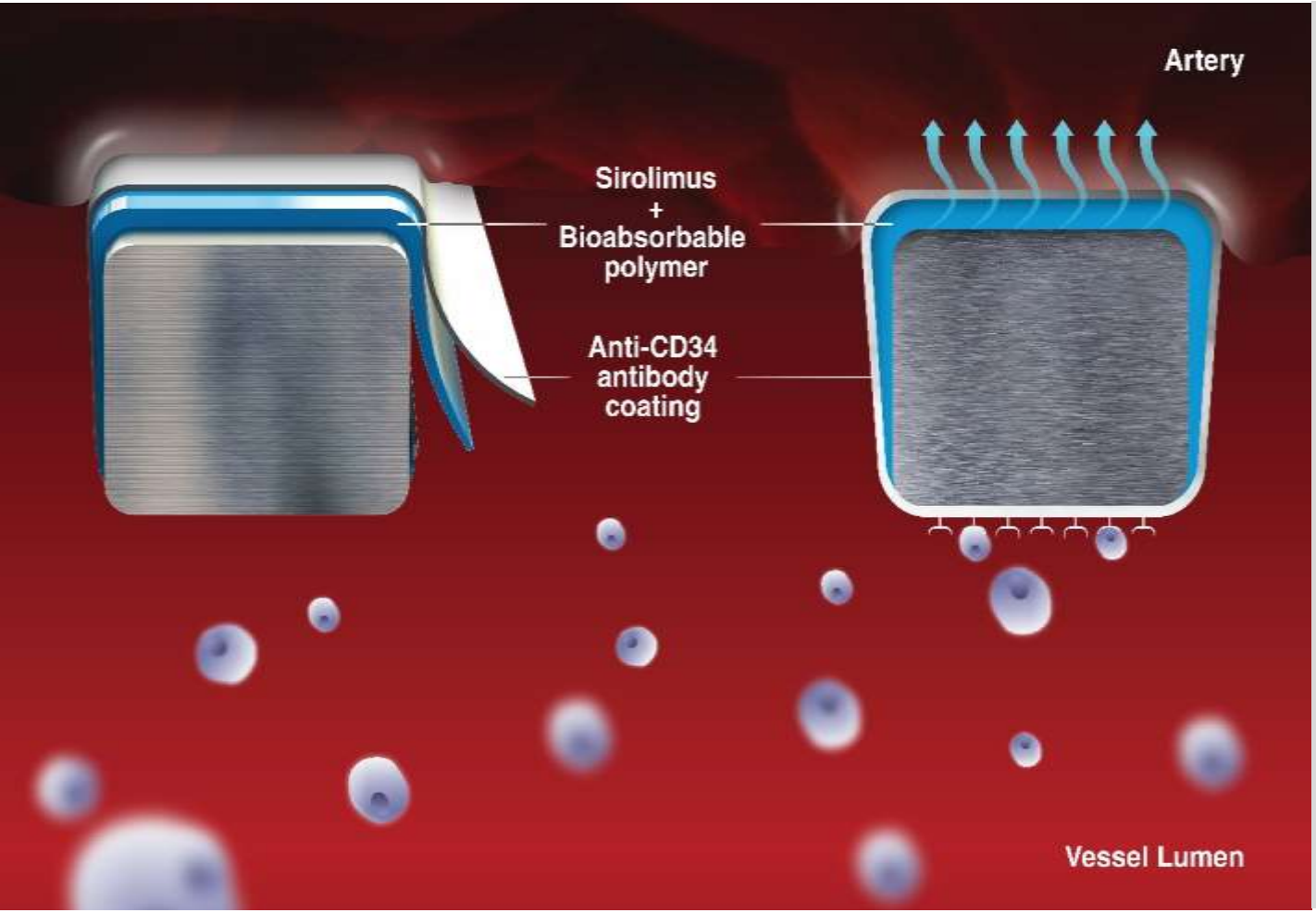
Disclosure Statement of Financial Interest

I, Stephen Rowland, am an employee of OrbusNeich Medical, Inc.

The COMBO Plus Dual Therapy Stent:
Abluminal Bioresorbable Drug Delivery with Luminal EPC Capture

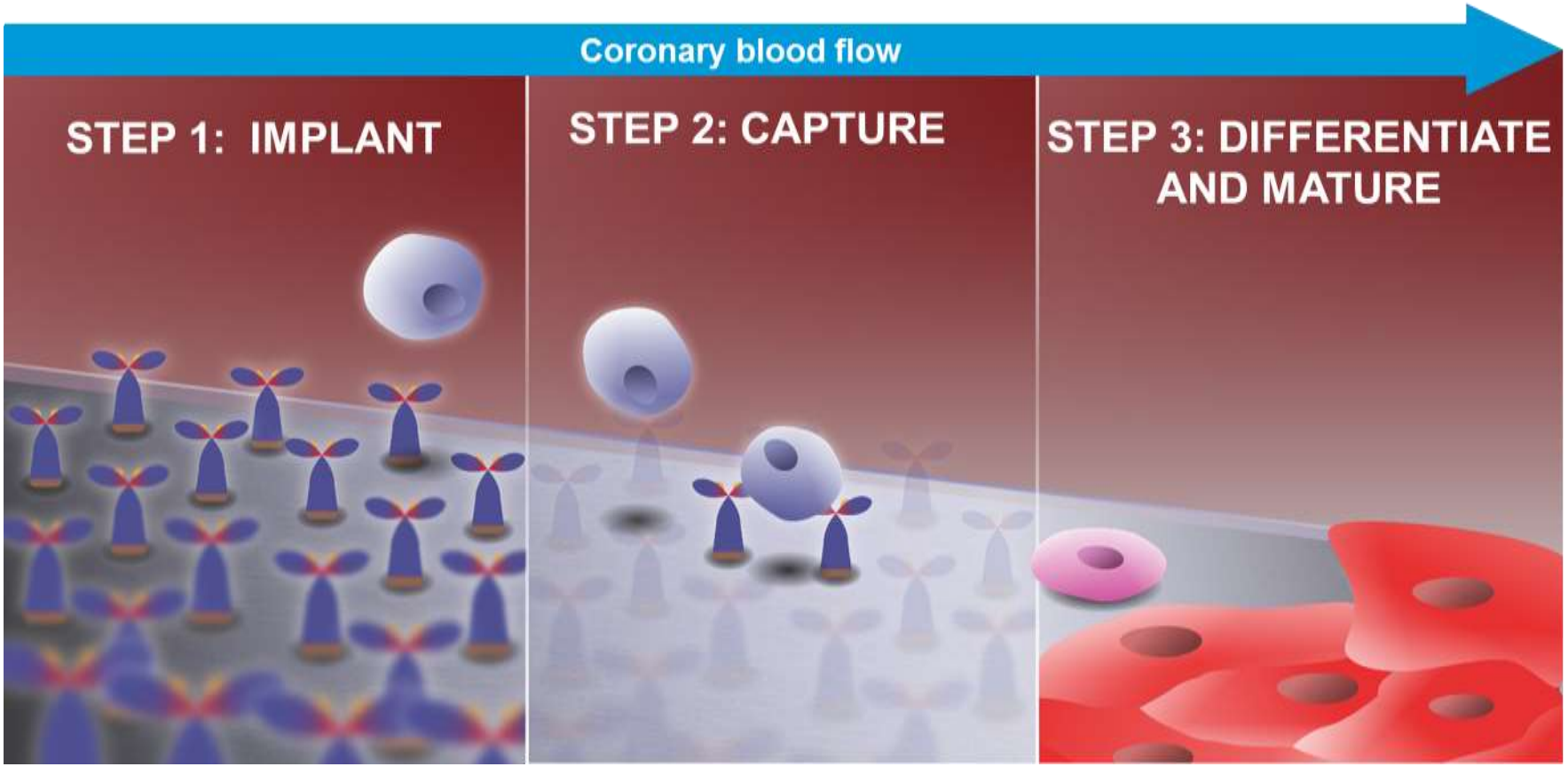


Stent & Delivery System
Highly conformable stent with excellent radial strength

Sirolimus & Polymer Matrix
Abluminal drug and bioabsorbable polymer matrix for control proliferation

CD34 Antibodies
Enable active capture of EPC for fast endothelial coverage

CD34 antibodies capture circulating EPCs which mature into functional endothelium



Following implantation, the immobilized CD34 antibodies are exposed to the circulating blood

Circulating endothelial progenitor cells (EPC) are captures by antibody

EPCs attach and differentiate into mature endothelial cells; an important step in re-establishing healthy neointima

HARMONEE

- HBD WG1 Global Clinical Trial
  - Adopted as Proof-of-Concept Project
- Single Protocol and Data Management
- Parallel trial approval process by PMDA & FDA
- Regulatory Objectives
  - Japan Shonin (market approval)
  - Satisfy US feasibility & invasive follow up requirements

Simultaneous Japan and US trial approval

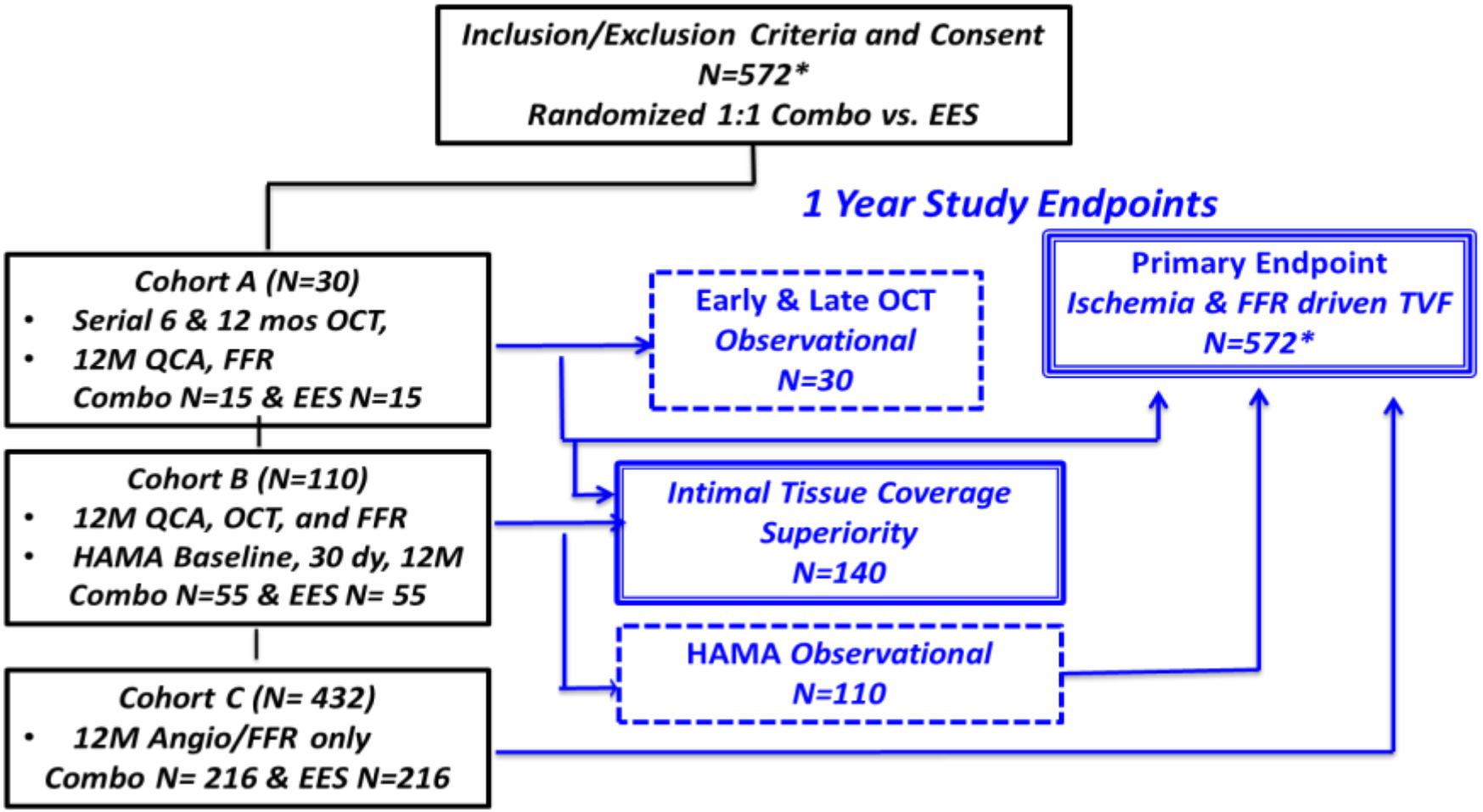
- Parallel consultation pathways
- Differing consultation processes
  - PMDA – formal presentation, informal consultations on areas of concern, formal submission
  - FDA – informal consultation, formal submission, formal consultations
- Global harmonization initiative – IMDRF
  - HBD experience invaluable preparation

Challenges in Trial Design

- Device Effectiveness
  - Clinical
  - Angiographic
  - Mechanistic
- Device Safety
  - Clinical
  - HAMA
- Differences in clinical practice

HARMONEE Study

Enrollment Cohort Flow Diagram



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

AHJ 187 112-121 2017; Kong et al.

HARMONEE Status

- Protocol CTN approval by PMDA
- IDE approval by FDA
- 33 Japan sites and 17 US sites
- Enrollment completed June 2016
    - Japan enrollment – 439 subjects
    - US enrollment – 133 subjects
- 12-month follow-up period
  - Completed July 2017
- Primary study results presented as a First Report in the Main Arena at TCT 2017

Harmonized Assessment by Randomized Multicenter Study of OrbusNEich's COMBO StEnt

The *HARMONEE* Primary Study Report

*Mitchell W. Krucoff MD, FACC, FAHA, FSCAI**

Professor of Medicine / Cardiology

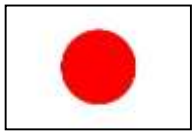
Duke University Medical Center

Director, Cardiovascular Devices Unit

Duke Clinical Research Institute

****on behalf of the Japan-USA HARMONEE investigators***

Enrollment & Follow-Up: ITT population



33 sites
439 pts (77%)

572 patients randomized

17 sites
133 pts (23%)

287 COMBO

285 EES

3 (1.0%) non-protocol stent

2 (0.7%) withdrew or lost to FU

2 (0.7%) non-protocol stent

6 (2.1%) withdrew or lost to FU

285 (99.3%) 1 year clinical FU

279 (97.9%) 1 year clinical FU

271 (95.1%) 1 year angio FU

261 (91.6%) 1 year FFR

262 (93.9%) 1 year angio FU

256 (91.8%) 1 year FFR

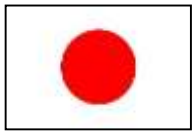
Cohort A&B 1 year OCT FU (n=70)

65 (92.9%)

Cohort A&B 1 year OCT FU (n=70)

63 (90.0%)

Enrollment & Follow-Up: ITT population



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1yr Clinical FU 98.6%

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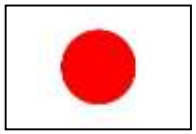

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Protocol Imaging
Angio FU 94.5%
FFR FU 91.7%
OCT FU 91.4%

2 (0.7%) withdrew or lost to FU

6 (2.1%) withdrew or lost to FU

285 (99.3%

clinical FU

271 (95.1%) 1 year angio FU

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Cohort A&B 1 year OCT FU (n=70)

63 (90.0%)

HARMONEE 12-mo Trial Results

- Efficacy
  - Met non-inferiority in 12-month Target Vessel Failure [TVF] with 7.0% rate in Combo versus 4.2% rate in EES (Non-inferiority margin 7%, non-inferiority p-value 0.020)
  - Combo 12-month late loss and binary restenosis were comparable to EES
  - Met superiority in 12-month healthy strut coverage by OCT with 91.6% in Combo versus 74.8% in EES (p-value <0.001)
- Safety
  - No HAMA conversion and no Stent Thrombosis in Combo
  - No unanticipated device-related adverse events
- Manuscript in preparation

Next Steps

HARMOMEE Trial

- "Deep Dives" into sub-set and imaging data sets
- Long-term follow-up out to 5 years

Japan

- Shonin Application
- PMS proposal

US

- Consultation on further trial requirements

HBD

HBD Harmonization By Doing

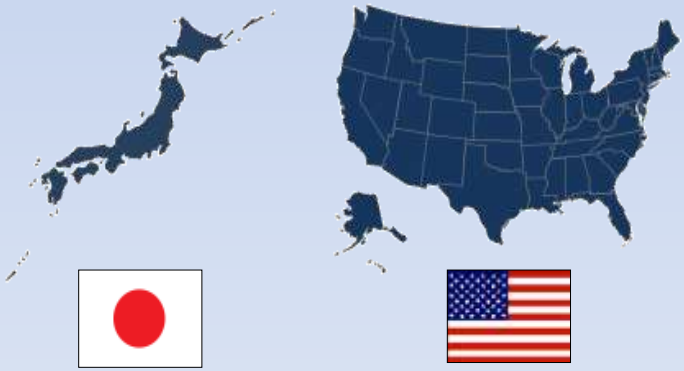
Benefits of Participation in HBD

Overcoming Real Challenges

- Internal organization - Alignment
- Clinical and regulatory objectives – Japan “First” Approach
- Trial approval in Japan and US - Simultaneous
- Site contracting & management - Best Practices
- Regional clinical practice - Protocol and Practice Guidelines
- Safety reporting requirements - Common Procedures

HARMONEE

Harmonized **A**ssessment by **R**andomized, **M**ulti-center Study
Of the **N**ov**E**l COMBO St**E**nt



HARMONEE Trial Organization

Study PIs	Shigeru Saito, Mitchell Krucoff
Study Chair	David F. Kong
Regional PIs	Shigeru Nakamura (Japan), Roxanna Mehran (USA)
Biostatistics	Hussein R. Al-Khalidi, Gudaye Tassisa
OCT Core	CRF: Akiko Maehara (Director)
FFR Core	CWR: Hiram Bezera (Director)
QCA Core	CRF: Philippe Généreux (Director)
DSMC	David Faxon (Chair), Alexandra Lansky, John Alexander, Taka Uchida, Jan Tijssen
CEC	Raj Mehta (Chair), Schuyler Jones (CEC-PI)
ARO	DCRI
SMO	DCRI, CMIC
Sponsor	OrbusNeich Medical, Ft Lauderdale and OMKK, Tokyo

Thank You

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