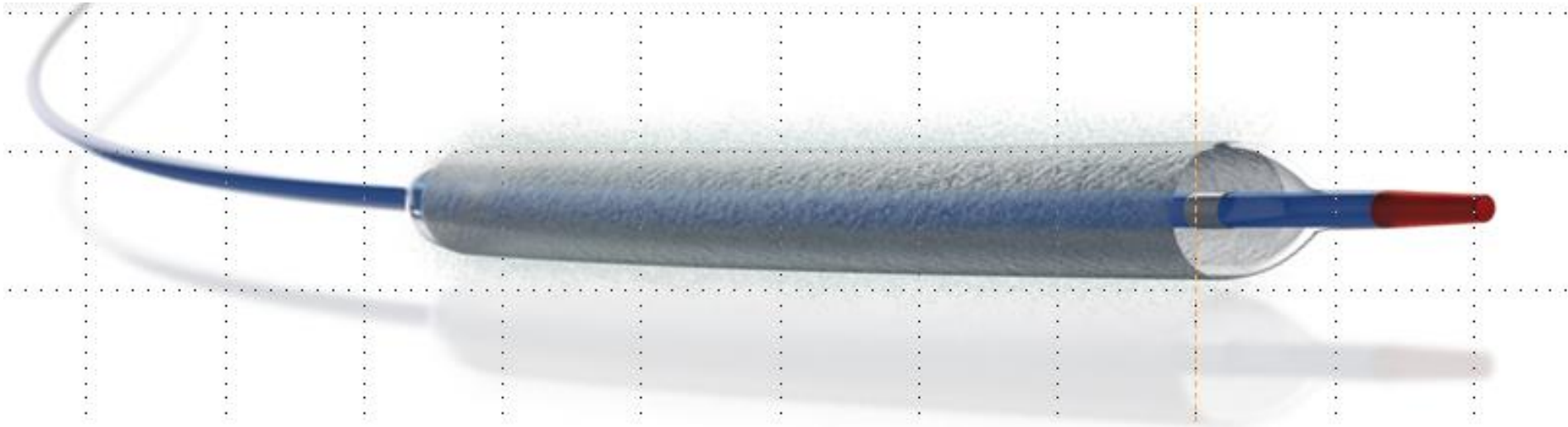
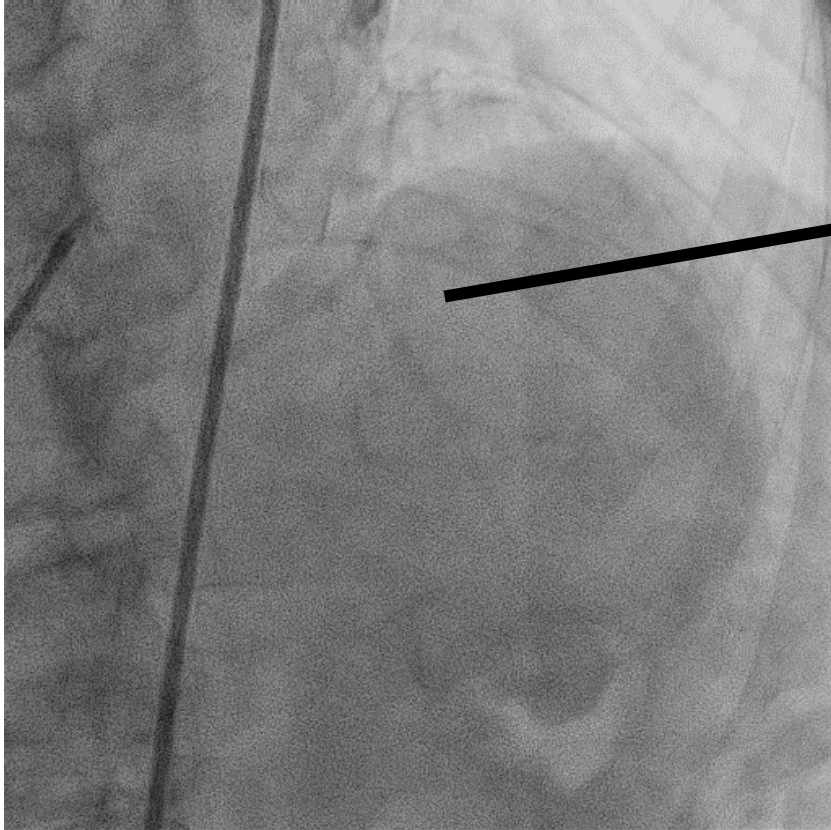


Leave the Right AGENT Behind : DCB Technology and Mechanism



Chung-Ang University Gwangmyeong Hospital, Heart Brain Hospital
Sang Yeub Lee

F/91 NSTEMI, HTN, DM, A.fib with NOAC

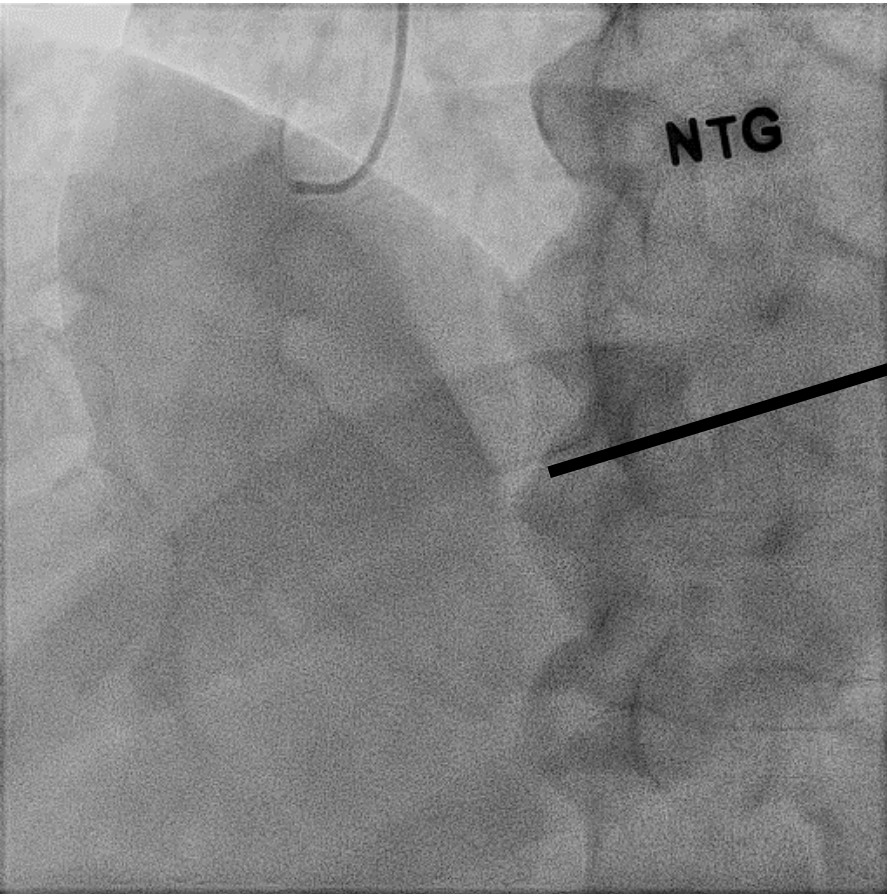


This bifurcated lesion, frail very old women with anticoagulation! What is your plan?

1. Just balloon angioplasty ?
2. Implant metal stent?
3. How about balloon angioplasty and drug delivery ?

→ **Drug coated balloon with side branch patency, shorter DAPT, no stent related issue**

M/58 Unstable angina, HTN



Bifurcated lesion and both main and side branch size comparable!
What is your choice?

1. **Metal stent with side branch compromise?**
2. **Drug coated balloon with nothing behind?**

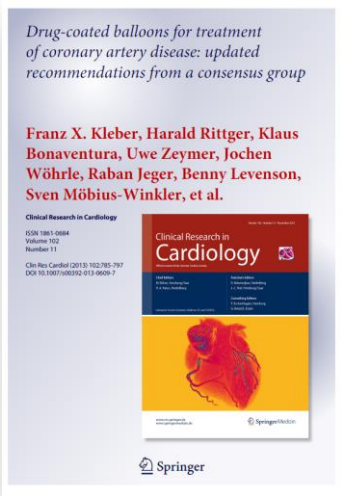
Practice Guidelines

ESC / EACTS Guidelines 2014^[1]

DCB and DES: Class IA Recommendation for ISR*

Restenosis			
Repeat PCI is recommended, if technically feasible.	I	C	
DES are recommended for the treatment of in-stent re-stenosis (within BMS or DES).	I	A	501,502,508 511,524
Drug-coated balloons are recommended for the treatment of in-stent restenosis (within BMS or DES).	I	A	507– 511,524
IVUS and/or OCT should be considered to detect stent-related mechanical problems.	IIa	C	

*BMS and DES ISR



DCB Consensus Group recommendation – 2013^[25]

- ISR (pre-dilatation or other lesion-preparation techniques recommended. Scoring or Cutting Balloons to be considered to avoid balloon slippage and facilitate complete stent expansion of restenosed stent)
- Any contraindications to prolonged DAPT
- Small vessels and Bifurcations remain potential, promising indications for DCB

Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauert e P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014;35:2541–2619

Kleber FX, Rittger H, Bonaventura K, Zeymer U, Wöhrle J, Jeger R, Levenson B, Möbius-Winkler S, Bruch L, Fischer D, Hengstenberg C, Pörner T, Mathey D, Scheller B. Drug-coated balloons for treatment of coronary artery disease: updated recommendations from a consensus group. Clin Res Cardiol. 2013 Nov;102(11):785-97; Adapted from Latib, A. TCT2019

Agent DCB is an investigational device in the United States and is not available for sale in the US.

Practice Guidelines

2018 ESC/EACTS Guidelines

13.4.1 Restenosis

Restenosis associated with angina or ischaemia should be treated by repeat revascularization, and repeat PCI remains the strategy of choice for most of these patients. In this setting, the results from DES are superior to those obtained with balloon angioplasty, BMS implantation, or brachytherapy.^{360–364}

For restenosis within BMS, drug-coated balloon (DCB) proved superior to plain balloon angioplasty^{365–367} and comparable to first-generation DES.^{365,366,368–372} One trial showed inferior angiographic outcomes in comparison to new-generation DES,³⁷³ while a second trial showed comparable outcomes.³⁷⁴ For restenosis within DES, DCBs also proved superior to plain balloon angioplasty^{367,369,371} and comparable to first-generation DES.³⁷¹ In one study, DCBs were inferior to new-generation DES in terms of the primary angiographic outcome measure.³⁷⁵ In a more recent study, including patients with any type of in-stent restenosis, outcomes between DCB and repeat stenting with new-generation DES were comparable.³⁷⁶ A single randomized trial of patients undergoing DCB for restenosis within DES showed superior angiographic outcomes in patients who underwent lesion preparation with scoring balloons vs. standard angioplasty balloons.³⁷⁷

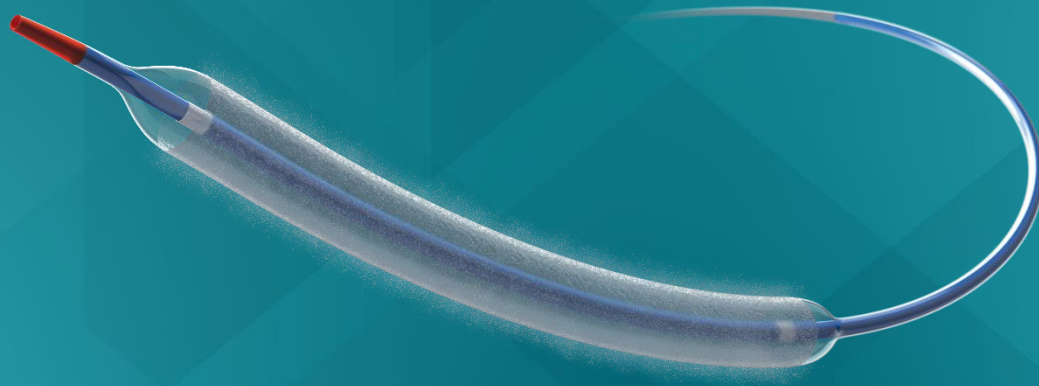
Network meta-analysis suggests that repeat stenting with new-generation DES (with EES) and DCB are ranked first and second as the highest efficacy treatments.^{378,379} The superior angiographic antirestenotic efficacy of new-generation DES should be weighed against a possible excess of long-term adverse events with repeat stenting during longer-term follow-up of these trials.^{380,381} However, observations in relation to clinical events must be interpreted with caution, as none of the trials was powered for clinical endpoints and the comparator stent in studies with long-term follow-up was an early-generation DES.

AGENT™

Paclitaxel Drug Coated Balloon

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Leave the Right AGENT Behind



Effortless
Deliverability



Efficient
Drug Transfer



Exceptional
Long-Term Outcomes

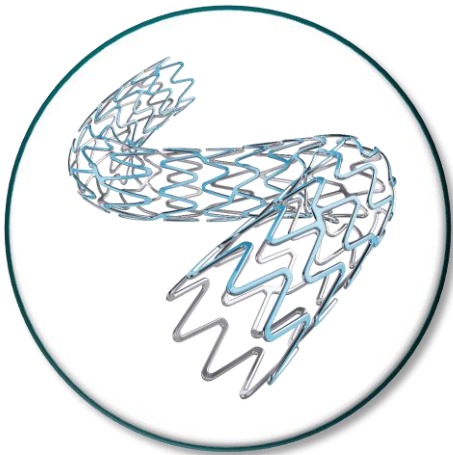
A Treatment Option for Every Lesion

SYNERGY MEGATRON™
Purpose-Built BP Stent

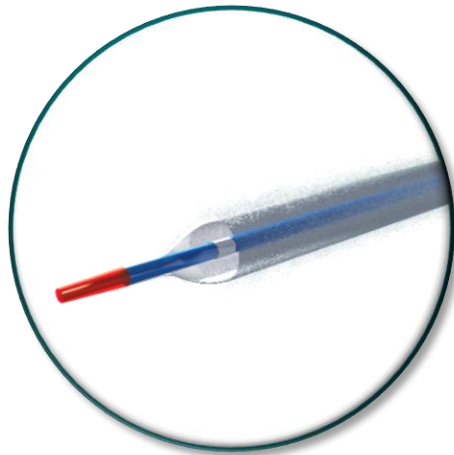


Large Vessels

SYNERGY™ XD
Next Gen BP Stent



AGENT™
Drug Coated Balloon



ISR
Small Vessel
Bifurcations



AGENT™ Drug Coated Balloon

Product Overview

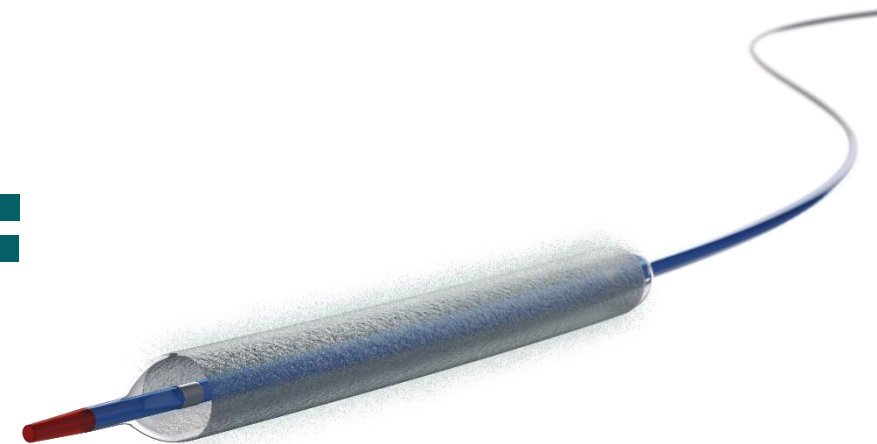
Agent combines the exceptional deliverability of the Emerge™ platform with the efficient drug transfer technology of TransPax™ coating



Emerge™
PTCA Dilatation Catheter



TransPax™
Coating Technology



Agent™

AGENT™ Drug Coated Balloon Key Features

Reliable Drug Transfer To Complex Distal Lesions

Unmatched Flexibility¹

Bi-segment inner shaft improves trackability in distal lesions



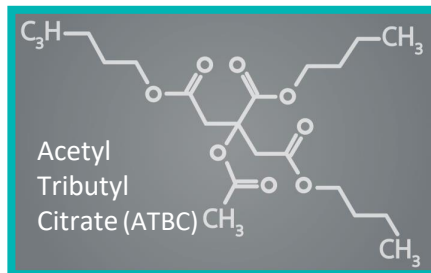
Unrivalled Profile²

Laser bonded tip improves crossability and reduced tip catch



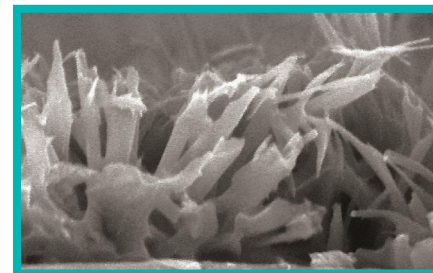
Targeted Transfer

Novel excipient maximizes balloon-to-target vessel transfer



Rapid Absorption

Sharp edge Ptx enhances tissue penetration



Sustained Retention

Crystalline formulation maintains therapy through the healing process



AGENT™
Paclitaxel Drug Coated Balloon

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Effortless Deliverability

Best-in-Class Flexibility

AGENT™ Drug Coated Balloon

Max Flexibility, Optimal Distal Delivery

AGENT Demonstrated Best Overall Flexibility

in bench testing¹

Catheter Flexibility

Flexibility comparison – 3.50mm DCB
(Lower is better)

Delivery force in vessel (g*cm)	AGENT	157
	Prevail	172
	Pantera Lux	207
	SeQuent Please Neo	190
	Magic Touch	246

Tip Flexibility

Flexibility comparison – 3.50mm DCB
(Lower is better)

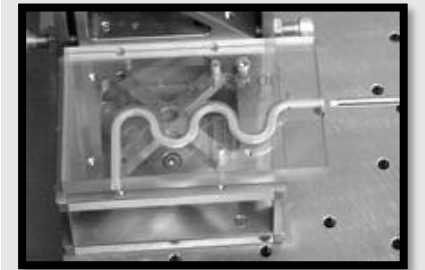
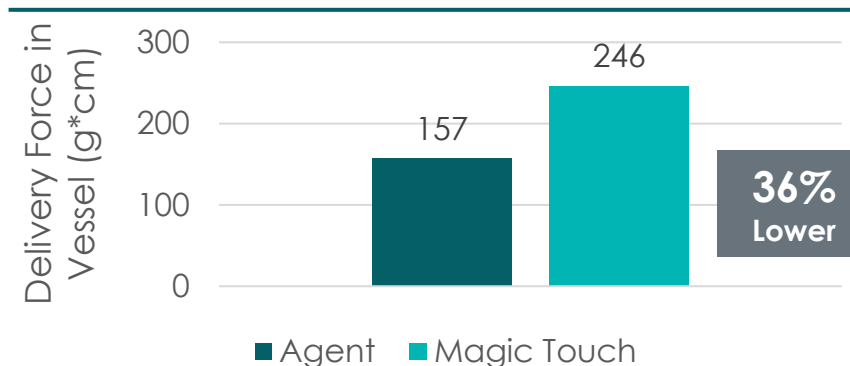
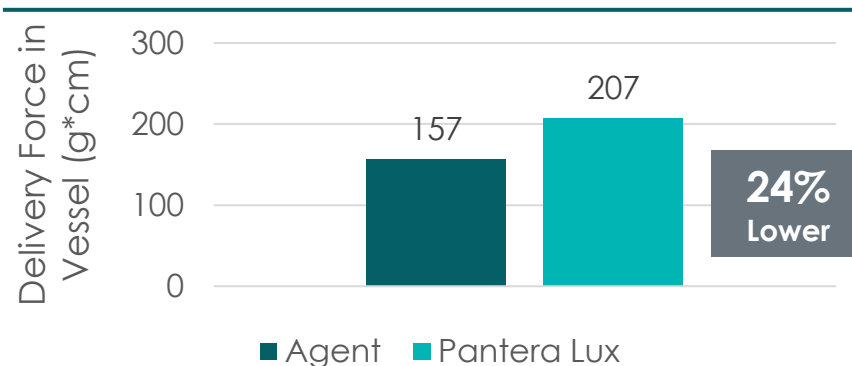
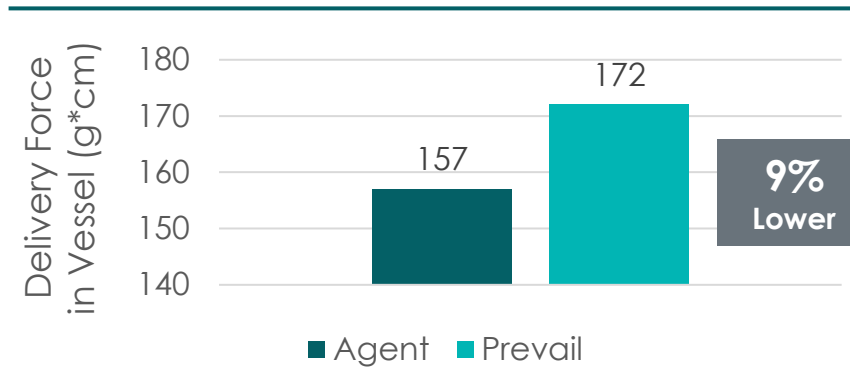
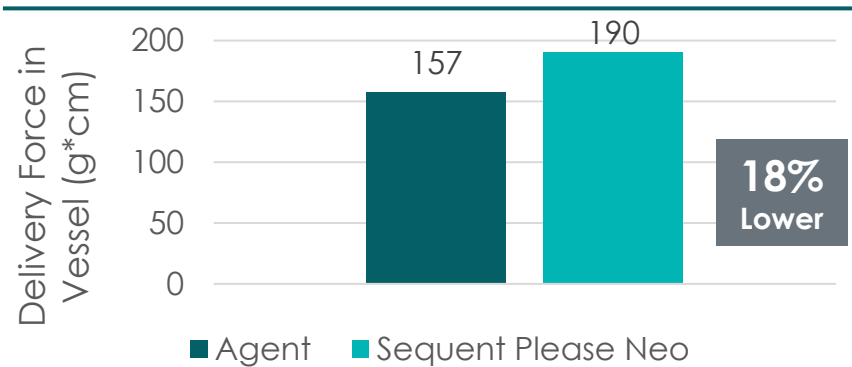
Max Force (g)	AGENT	76
	Prevail	88
	SeQuent Please Neo	150
	Pantera Lux	176
	Magic Touch	236

AGENT™ Drug Coated Balloon Catheter Flexibility Bench Test Data

Best-in-Class Catheter Flexibility

Lowest Delivery Force Compared to SeQuent Please Neo™, Prevail™, Magic Touch™ and Pantera Lux™¹

LOWER IS BETTER



Amount of delivery force (work/energy) required to track distal portion of catheter 10cm into arterial model

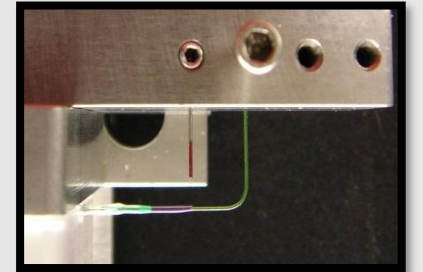
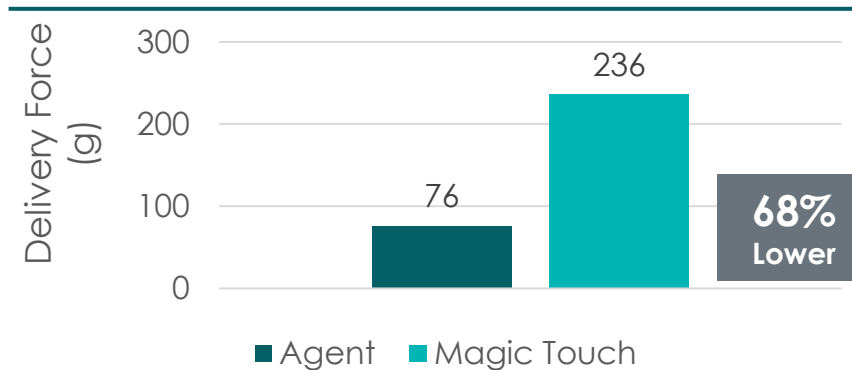
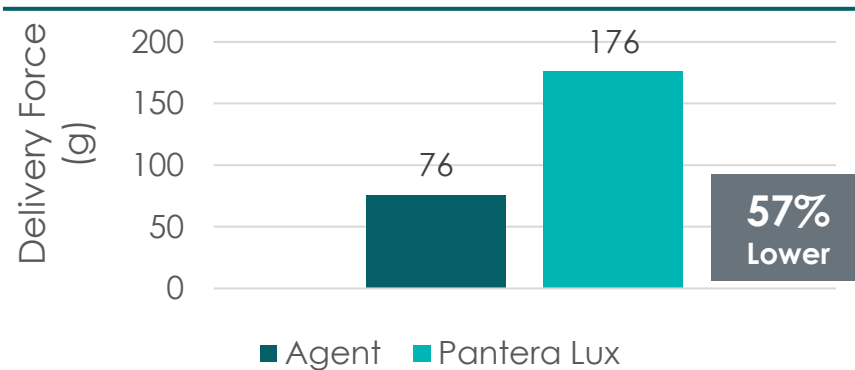
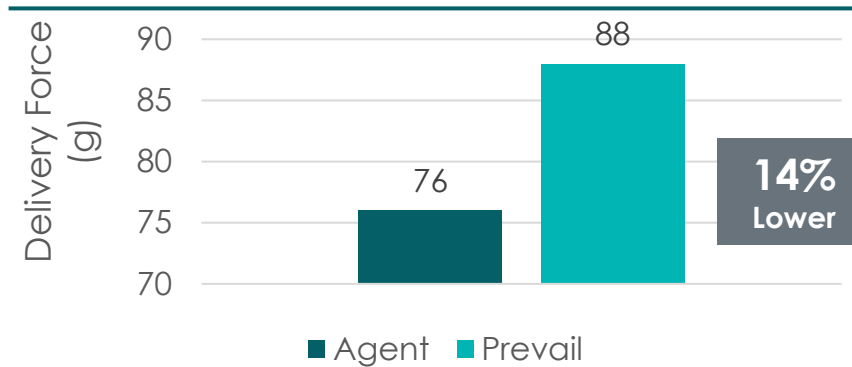
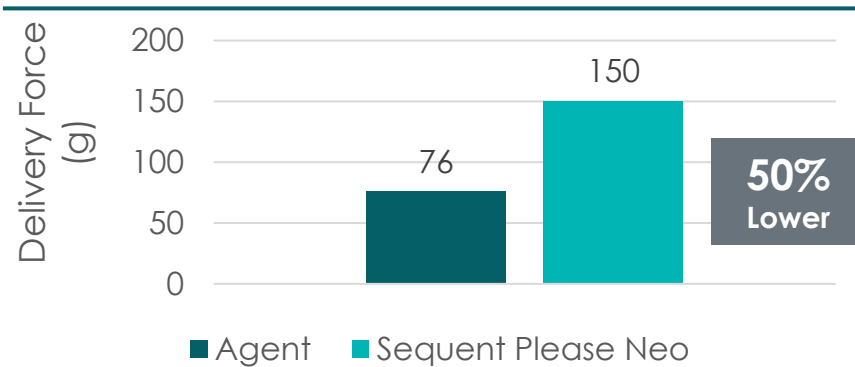
AGENT™ Drug Coated Balloon

Tip Flexibility Bench Test Data

Unmatched Tip Flexibility

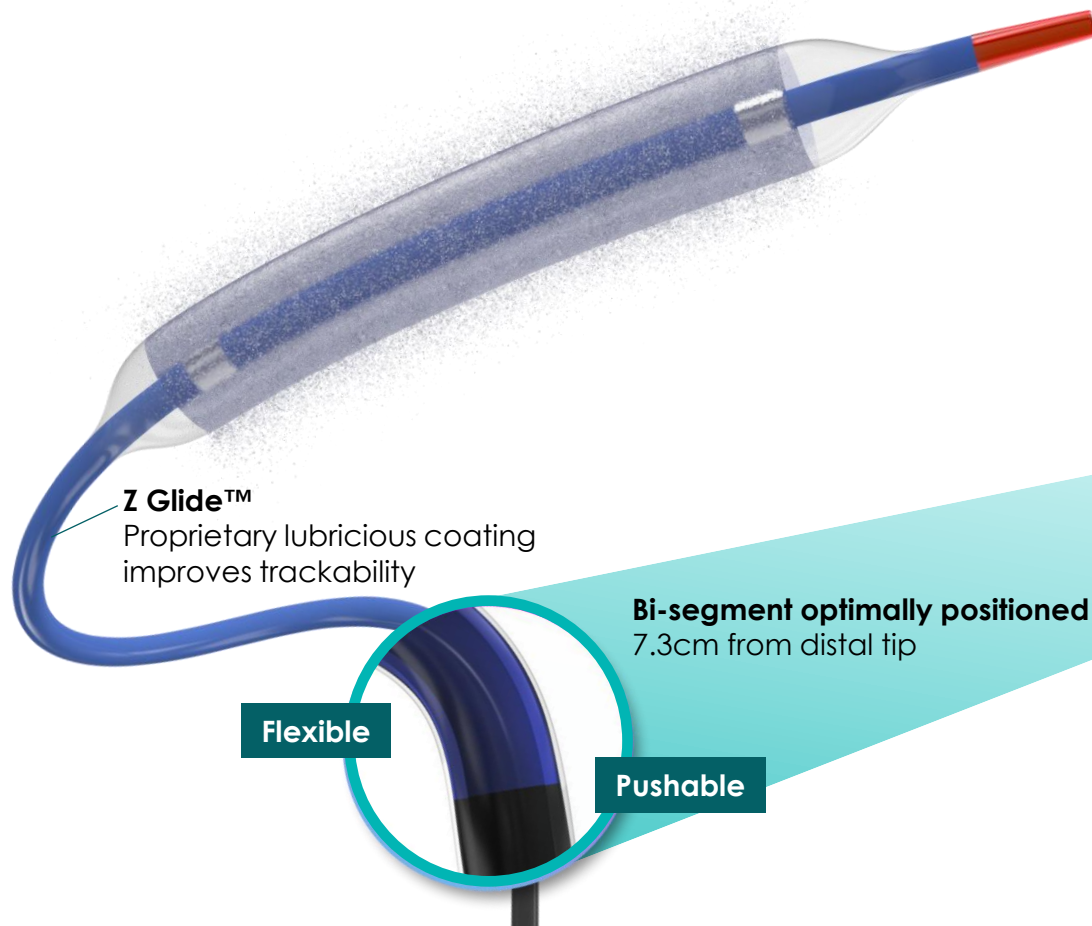
Lowest Delivery Force Compared to SeQuent Please Neo™, Prevail™, Magic Touch™ and Pantera Lux™

LOWER IS BETTER

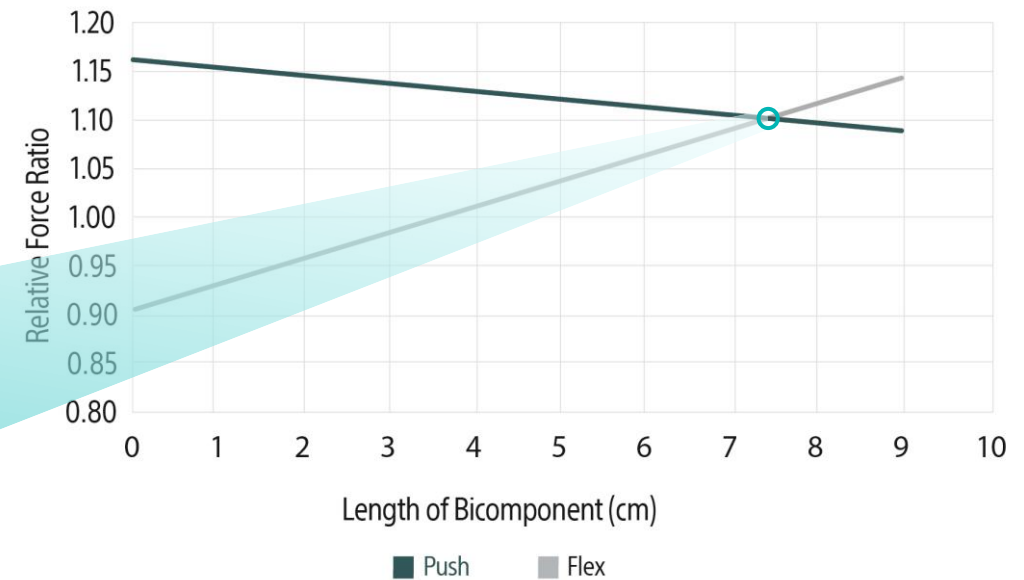


Maximum force
required to push
tip around
90° bend

Dual Polymer Bi-Segmented Inner Shaft Designed and Positioned to Optimize Flexibility and Pushability



Flexibility vs. Pushability



AGENT™
Paclitaxel Drug Coated Balloon

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Effortless Deliverability

Ultra-Low Profile

AGENT™ Demonstrated Best Overall Profile

in bench testing¹

1. Distal Bond Profile

Tip profile comparison –
3.50mm DCB (Lower is better)

Distal Bond Profile (inches)

AGENT	0.027
Prevail	0.028
Pantera Lux	0.031
SeQuent Please Neo	0.032
Magic Touch	0.037

2. Lesion Entry Profile

Tip profile comparison –
3.50mm DCB (Lower is better)

Lesion entry profile (inches)

AGENT	0.016
SeQuent Please Neo	0.017
Prevail	0.017
Pantera Lux	0.018
Magic Touch	0.020





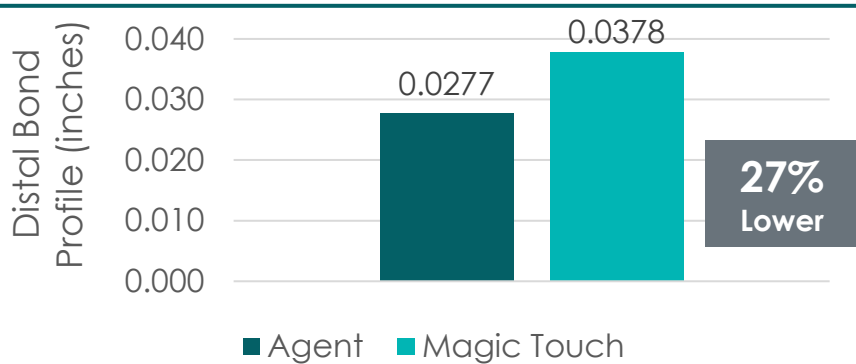
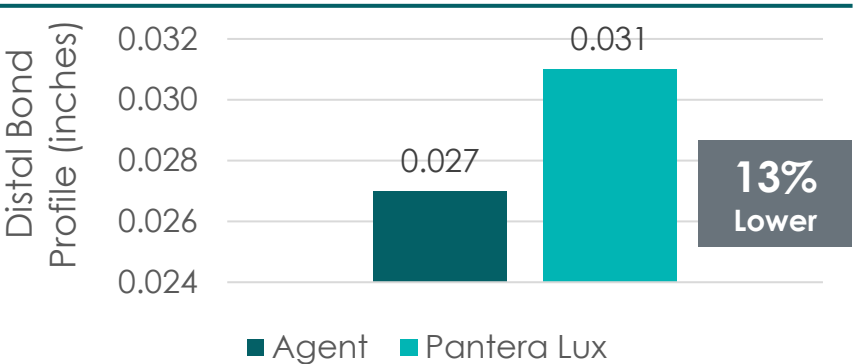
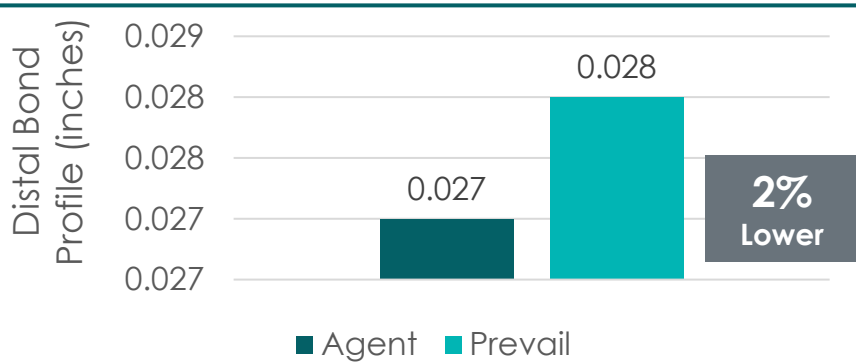
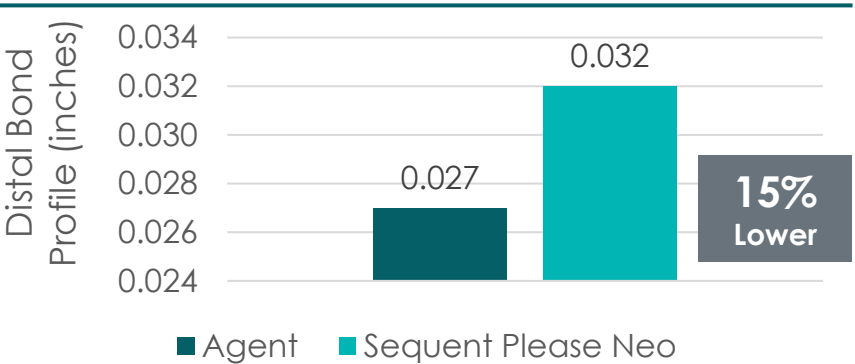
AGENT™ Drug Coated Balloon

Distal Bond Profile Bench Test Data

Best-in-Class Distal Bond Profile

Compared to SeQuent Please Neo™, Prevail™, Magic Touch™ and Pantera Lux™

LOWER IS BETTER



Measures the widest diameter between the very tip of the catheter and balloon waist transition

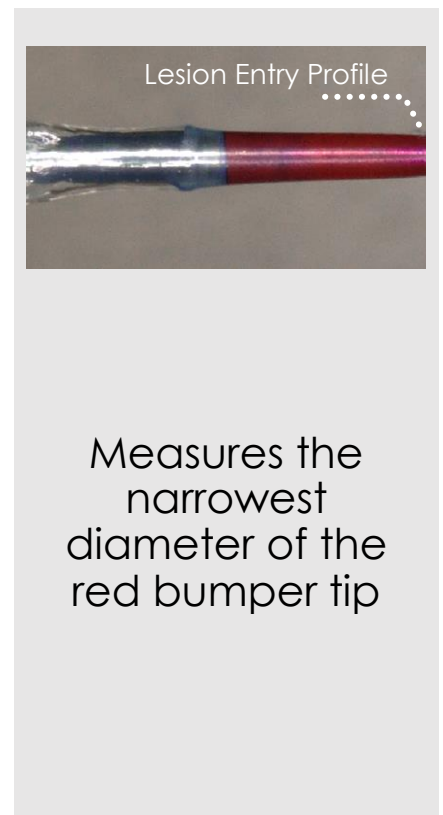
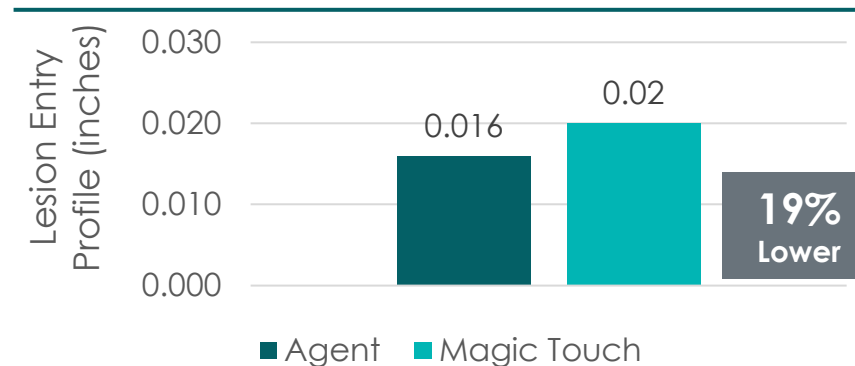
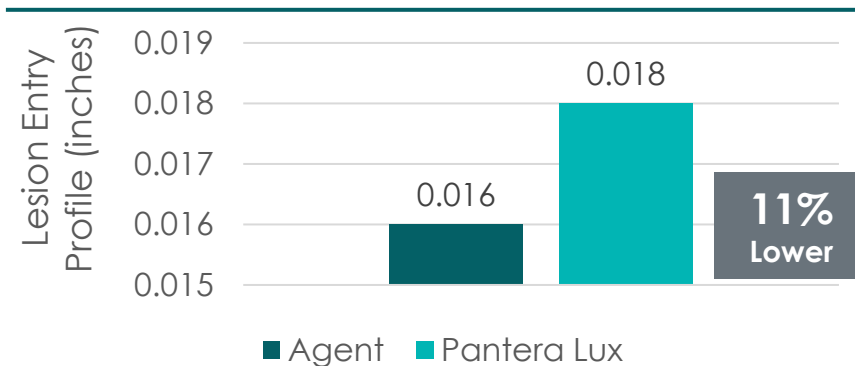
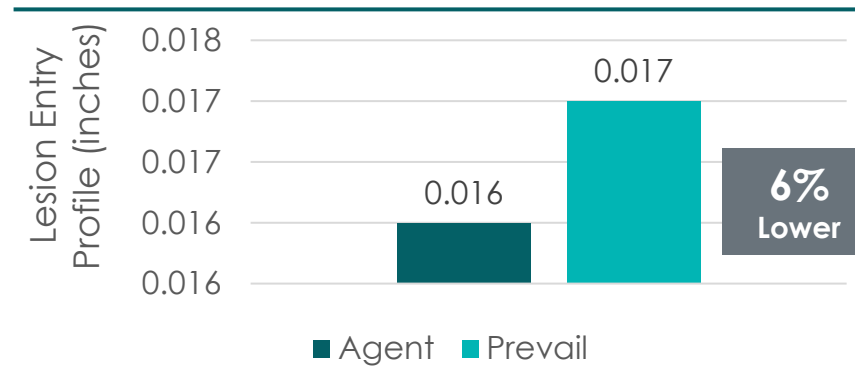
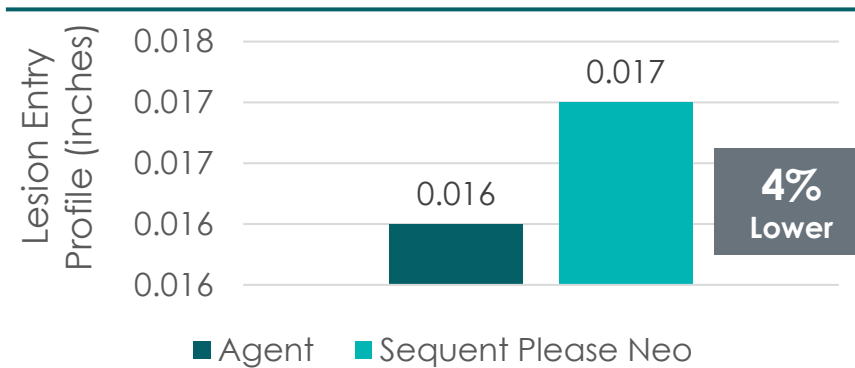
AGENT™ Drug Coated Balloon

Lesion Entry Profile Bench Test Data

Unmatched Lesion Entry Profile

Compared to SeQuent Please Neo™, Prevail™, Magic Touch™ and Pantera Lux™¹

LOWER IS BETTER



Laser bonded tip lowers profile for improved crossability in complex lesions



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Paclitaxel Drug Coated Balloon

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Efficient Drug Transfer

Technology Overview

AGENT™ Drug Coated Balloon TransPax™ Coating Introduction



TransPax™ Coating

Low balloon
Ptx load at
2ug/mm2



Novel Excipient
Acetyl Tributyl
Citrate (ATBC)



Proprietary
Coating
Technology



TransPax™

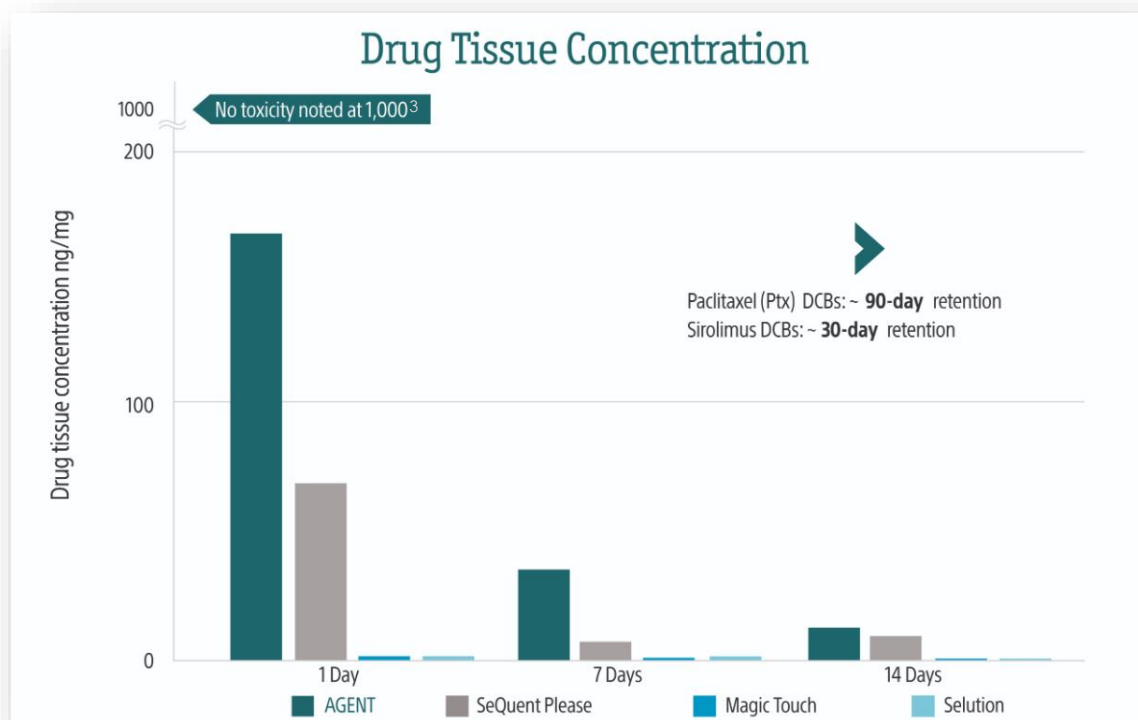


AGENT™ Drug Coated Balloon

Targeted and Efficient Drug Transfer

AGENT™ Achieved Higher Acute Tissue Concentrations Despite Low Balloon Ptx Load

in pre-clinical testing²



Lowest balloon drug load¹

AGENT:
2 ug/mm²

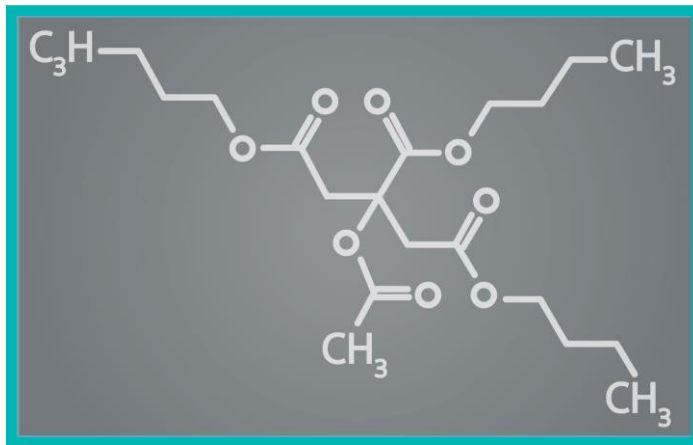
Other Ptx DCBs:
3-3.5 ug/mm²

1. Dose is calculated based on balloon diameter, length and dose density. 2. Pre-clinical pharmacokinetic studies performed using the same FDA recommended and accepted porcine coronary de novo vessel test method BSC conducted AGENT, SeQuent Please and Selution. Magic touch published data, TCT 2020. 3. Blagosklonny et al. Paclitaxel induces primary and postmitotic G1 arrest in human arterial smooth muscle cells. Cell Cycle. 2004 Aug;3(8):1050-6. Epub 2004 Aug 24. *Independent studies performed using the same FDA recommended and accepted porcine coronary de novo vessel test method. BSC conducted AGENT, SeQuent Please and Selution. Magic touch published data, TCT 2020.

Three Design Features Function Together to Provide Reliable Drug Transfer

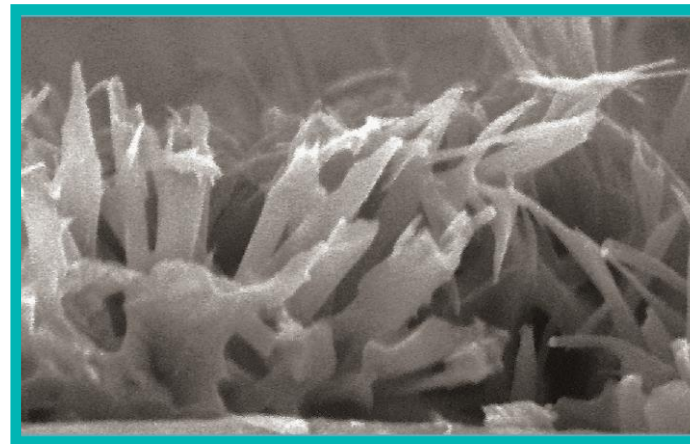
Phase 1: Targeted Transfer

Novel excipient maximizes
balloon-to-vessel transfer



Phase 2: Rapid Absorption

Sharp edge lipophilic Ptx
enhances tissue absorption



Phase 3: Sustained Retention

Crystalline formulation maintains
therapy through healing process



No Delivery Time Limit

AGENT™
Paclitaxel Drug Coated Balloon

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Efficient Drug Transfer

Targeted Transfer



Targeted DCB Drug Transfer

Importance of a Balanced Excipient

AGENT Excipient ATBC Maximizes Balloon-to-Target Vessel Transfer¹

Hydrophilic Loves water/low adhesiveness	SeQuent Please Neo™ Iopromide Prevail™ Urea AGENT™ ATBC Pantera Lux™ BHTC												Hydrophobic Dislikes water/highly adhesive
	●	●	●	●	●	●	●	●	●	●	●	●	
Low	Drug durability during delivery												High
High	Particulate loss downstream												Low
High	Ease of vessel wall transfer during inflation												Low



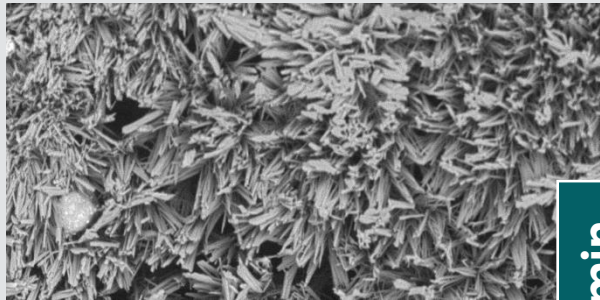
No delivery
time
limitation



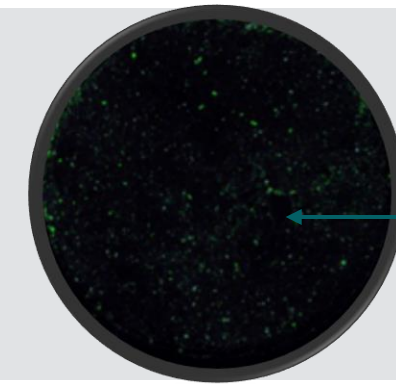
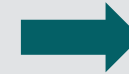
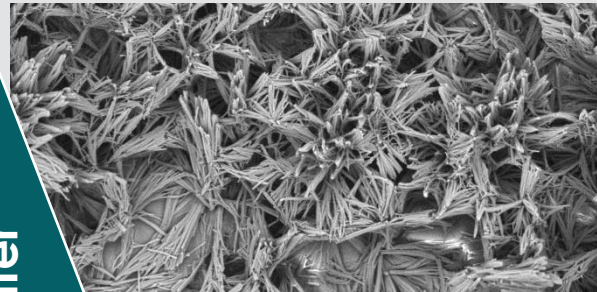
AGENT Demonstrated Best Overall Durability Under Hydration¹

More
Durable

AGENT



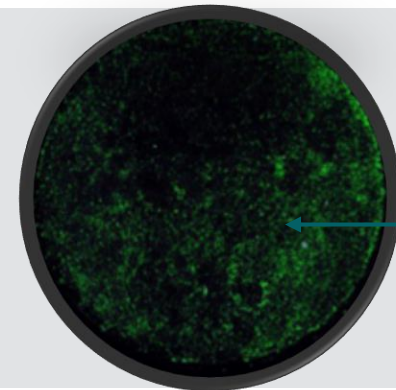
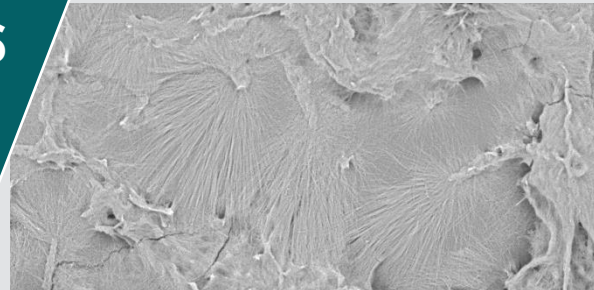
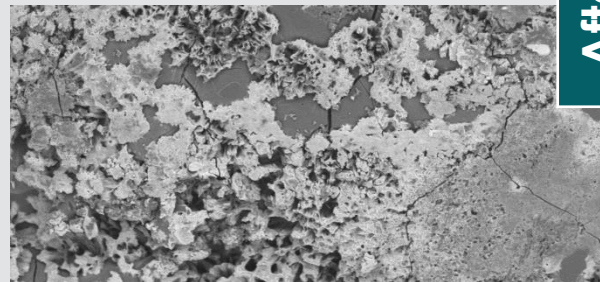
After 10 min
37°C Water



Fewer Particulate
Loss

Less
Durable

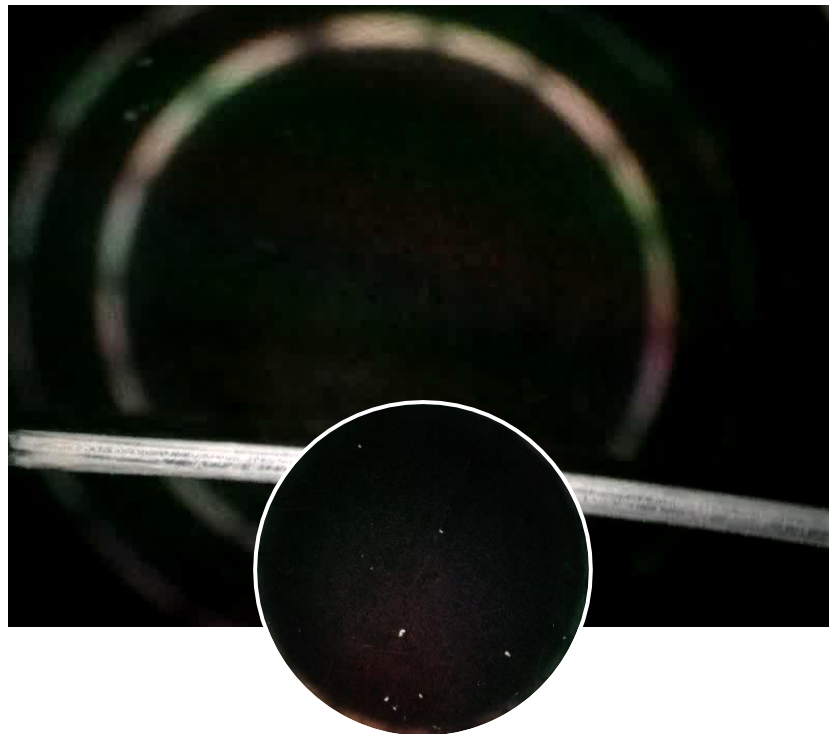
SeQuent
Please



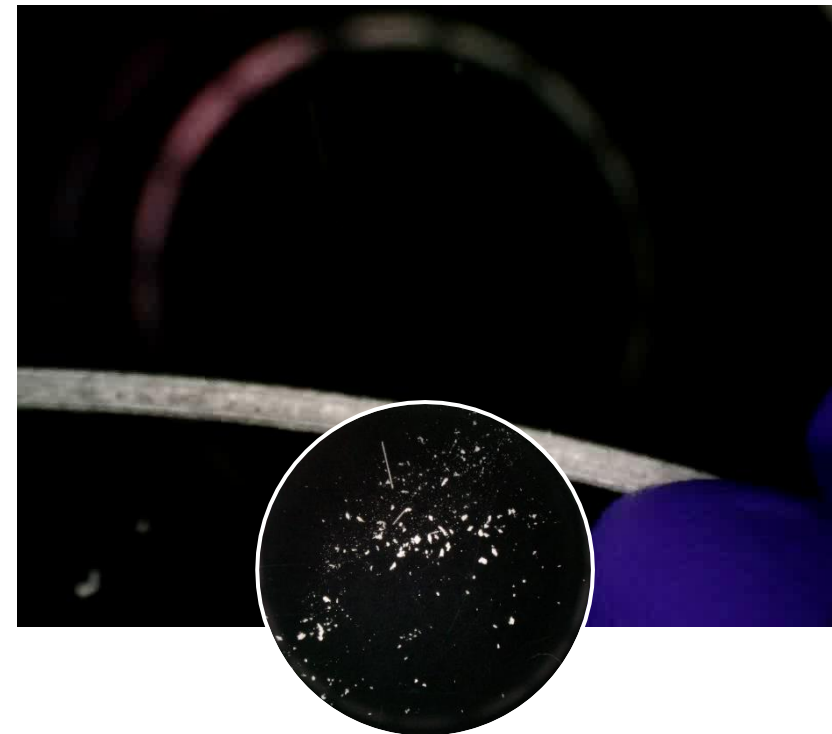
More Particulate
Loss

AGENT Demonstrated Best Overall Durability During Manual Manipulation¹

AGENT



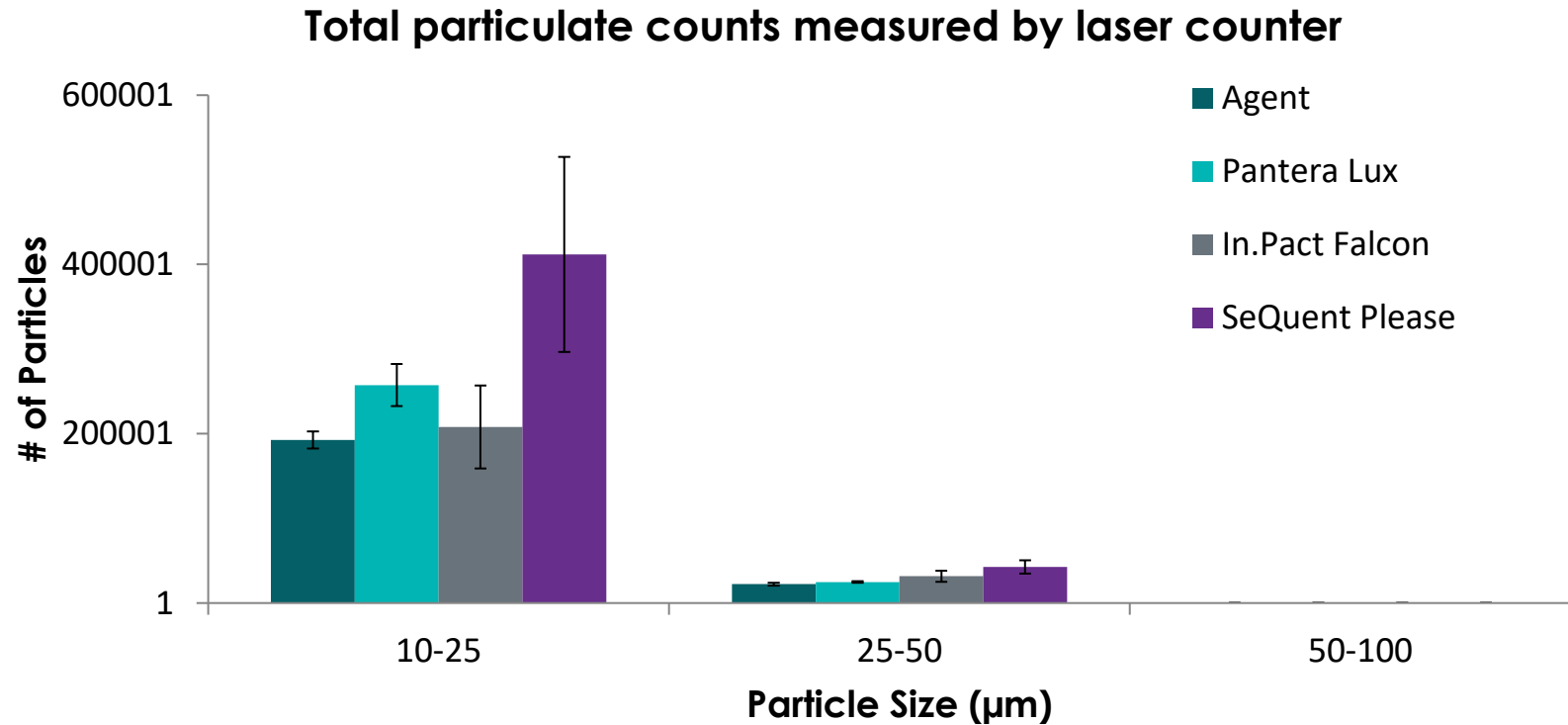
SeQuent Please



Particulate
capture test
using a 5
µm filter

AGENT Demonstrated Fewest Downstream Particulates¹

During tracking, deployment and withdrawal



Particulate count in circulation after track, deployment and retraction in simulated coronary anatomy model

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Paclitaxel Drug Coated Balloon

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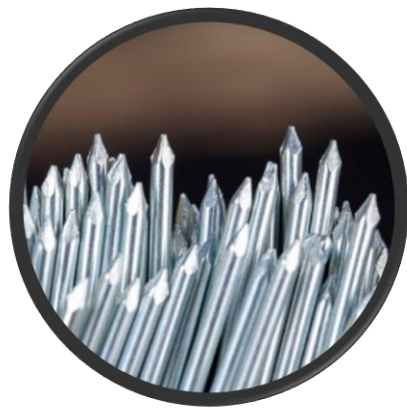
Efficient Drug Transfer

Rapid Absorption

DCB Tissue Absorption Data

Importance of Sharp Edge Drug Coating

Significantly Faster Absorption When DCB Drug is Formulated With Sharp Edges¹



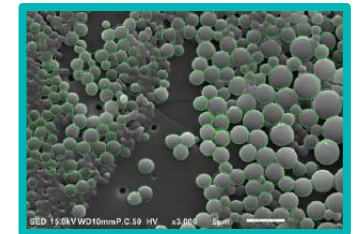
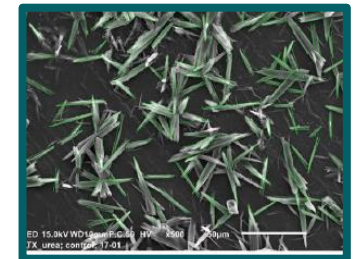
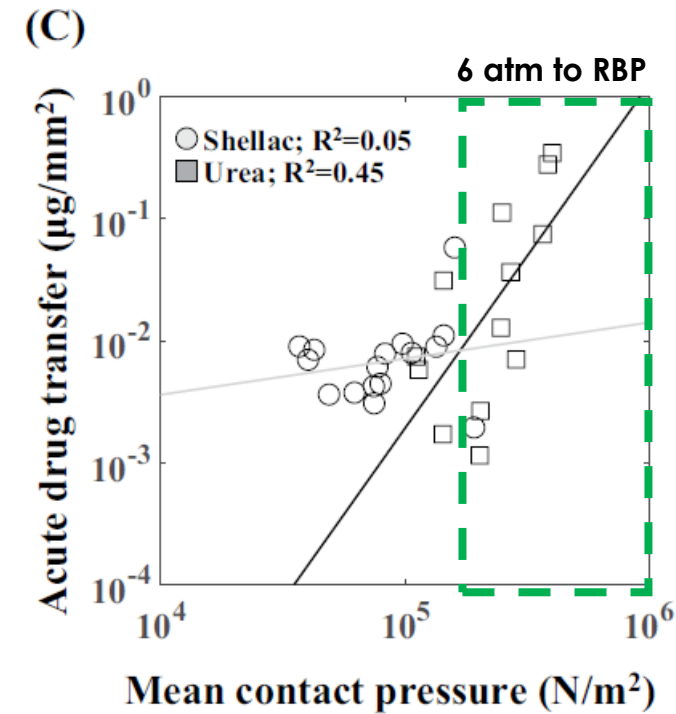
Steel Nails

VS



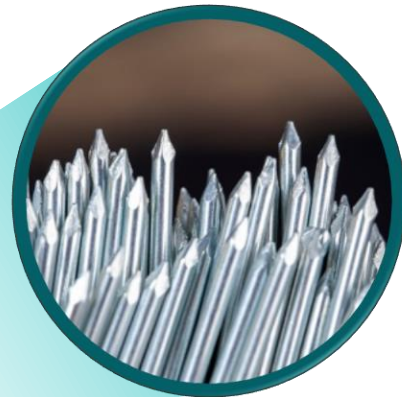
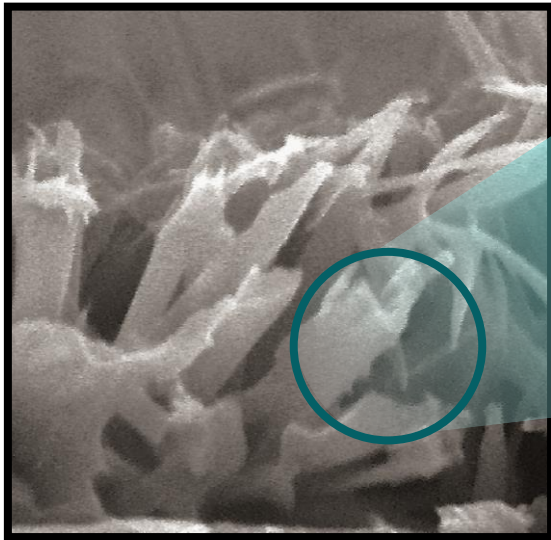
Steel Ball Bearings

Same material, which shape will pass through a hard surface easier?



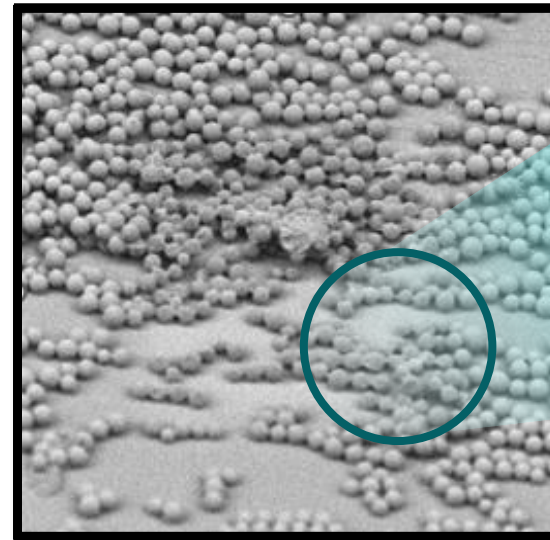
AGENT is Formulated With Sharp Edge Paclitaxel to Accelerate Absorption

Sharp Edge Paclitaxel (High Acute Tissue Absorption)



AGENT™

Rounded Paclitaxel (Low Acute Tissue Absorption)



Selution™

AGENT™
Paclitaxel Drug Coated Balloon

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Efficient Drug Transfer

Sustained Retention



DCB Drug Retention Data

The Importance of Crystalline Formulation

Significantly Slower Dissolution Rate When the DCB Drug Coating is Formulated Into Crystalline Structure¹



Sugar Crystals

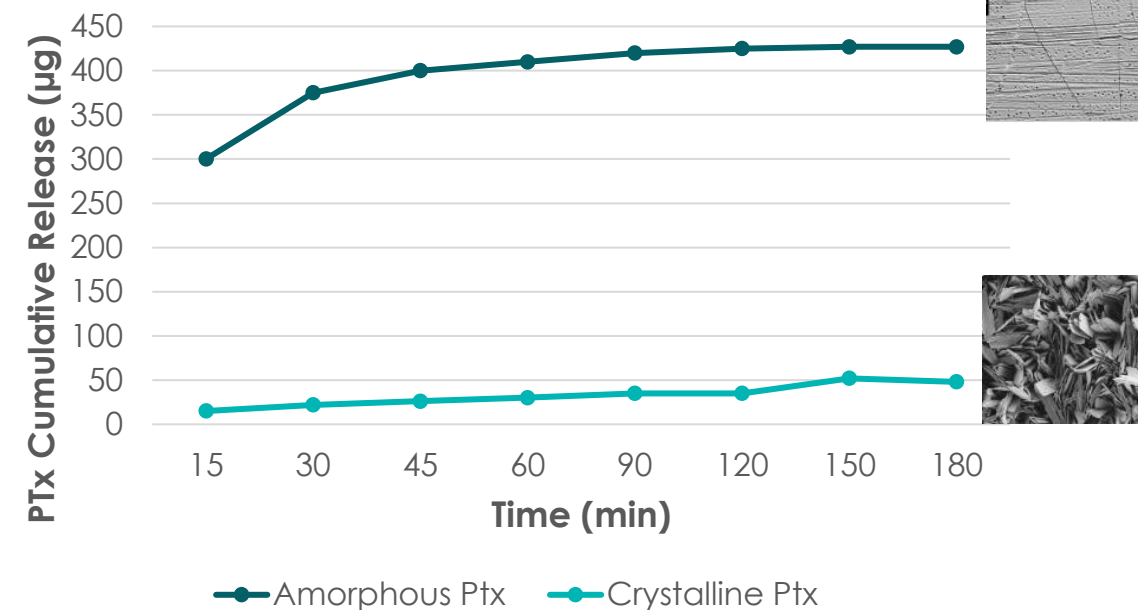
VS



Cotton Candy

Same material, which one dissolves slower?

DEB Dissolution Profile



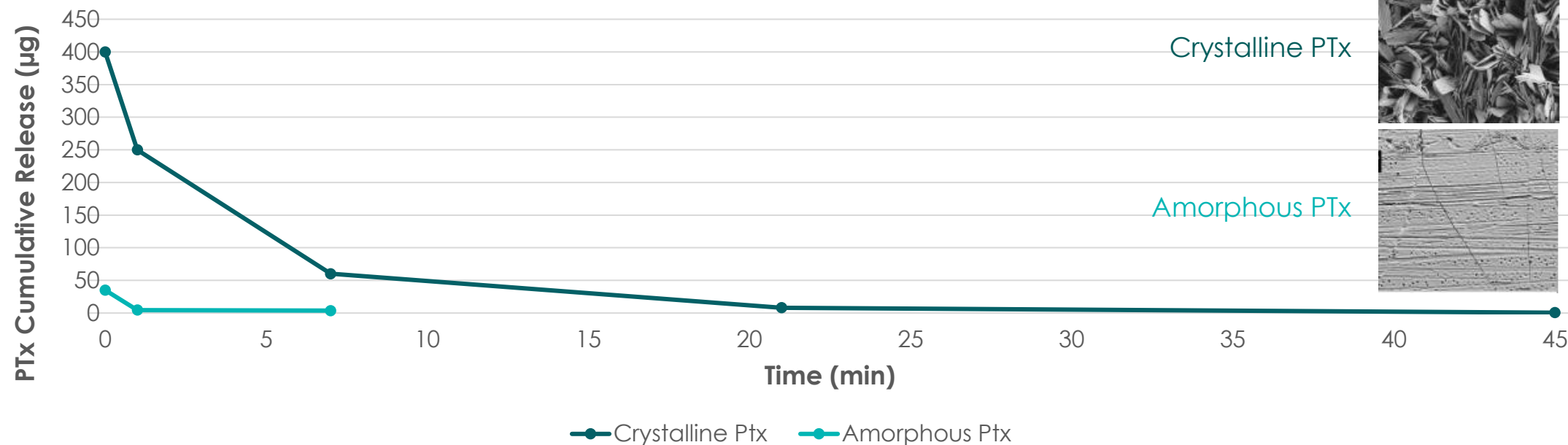


DCB Drug Retention Data

The Importance of Crystalline Formulation

Significantly Higher and Longer Sustained Ptx Tissue levels When the DCB Drug Coating is Formulated Into Crystalline Structure¹

In vivo Coronary Arterial Vessel Ptx Concentration

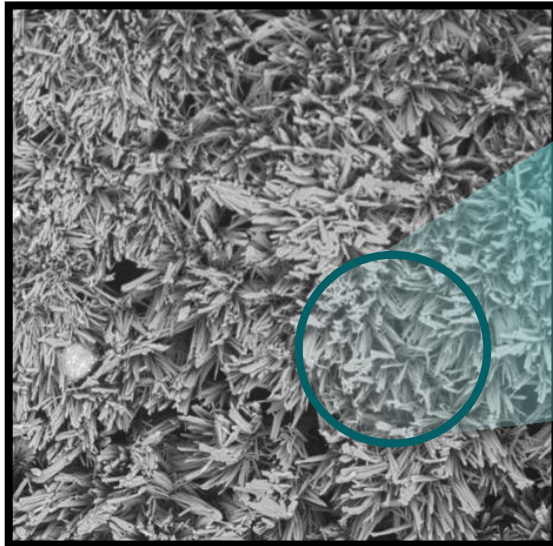


AGENT™ Drug Coated Balloon

Sustained Drug Retention

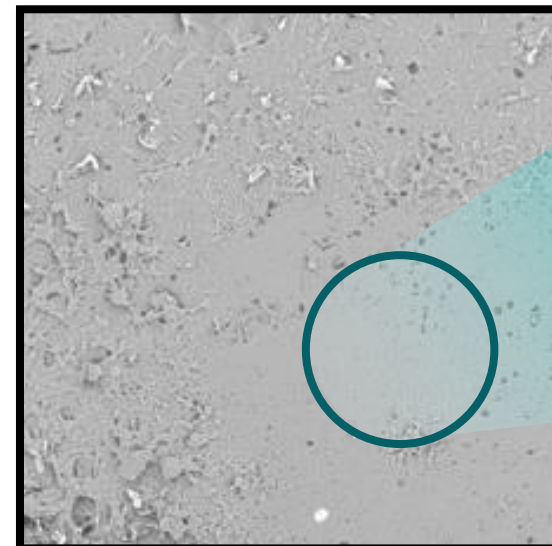
TransPax™ Coating Formulated Into a Durable Crystalline Structure for Sustained Retention

High Crystallinity (Difficult to Dissolve)



AGENT™

Low Crystallinity (Easy to Dissolve)



Prevail™

AGENT™
Paclitaxel Drug Coated Balloon

**Boston
Scientific**
Advancing science for life™



Exceptional Long-Term Outcomes

AGENT™ Clinical Data

AGENT DCB Clinical Strategy

Available Evidence & Ongoing Trials

Robust Clinical Program Addressing a Wide Spectrum of Cardiovascular Complexity

Over 4,500 Patients Studied

In-stent restenosis	De Novo Lesions	Patient-specific	Small Vessels	Bifurcations	Large Vessel	Complex Lesions
AGENT ISR, (RCT) N=125 ISAR DESIRE AGENT 3A, N=125 Agent-Ptx – Italian Multicenter Registry, N=354 APAC Registry* – TBD 2023, N=500 AGENT US IDE* – TBD 2024 – US indication, N=600, RCT Agent DCB real-world registry*, N=2000, all-comers, TLF at 1yr	AGENT De Novo All-comers Registry, N=338 Agent-Ptx – Italian Multicenter Registry, N=354 NATURE*, (RCT) N=200, all-comers, exclusion CTO, STEMI, Bif, Superiority CB+DCB vs. POBA+DCB Agent DCB real-world registry*, N=2000, all-comers, TLF at 1yr DCB UK/Ireland Registry*, N=3000, Feb 2023 approval	ACS: AGENT De Novo All-comers	AGENT Japan SV, (RCT) N=150	Agent-Ptx Italian, DCB UK/Ireland Registry*	Agent-Ptx Italian	Co-CTO* – TBD 2024, N=154

*On-going trials



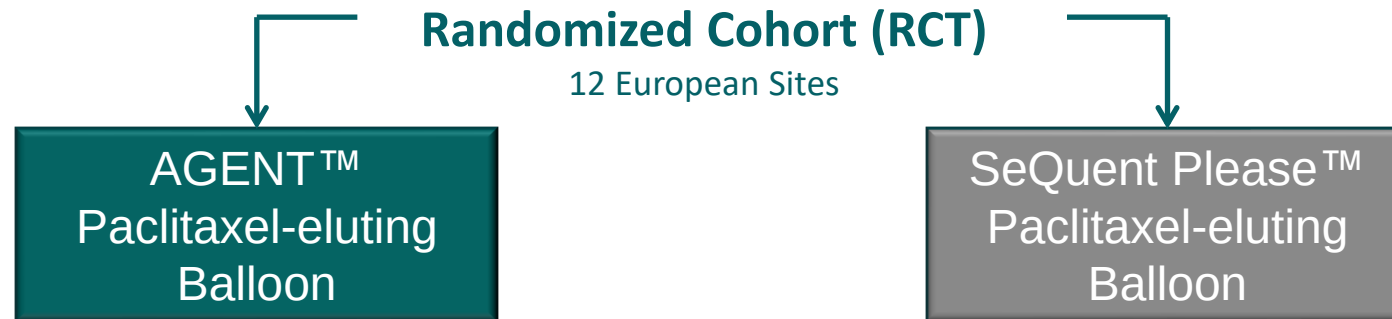
AGENT™ ISR Study

Trial Design

Patients with in-stent restenosis of a lesions previously treated with a BMS or DES

Lesion in native coronary artery with length ≤ 28 mm, RVD ≥ 2.0 mm ≤ 3.5 mm, and %DS $\geq 50 < 100\%$ if symptomatic

Excluded bifurcation, LM, SVG, total occlusion, recent PCI, acute MI



RCT Design

Multicentre noninferiority trial

1:1 randomization of 122 patients

Primary Endpoint: In-stent late loss at 6 mo

Clinical follow-up through 3 years

Dual antiplatelet therapy recommended for 3 months with a minimum of 4 weeks; indefinite ASA

* One-Year outcomes from a randomized multicenter study of two drug-coated balloons for the treatment of coronary in-stent restenosis

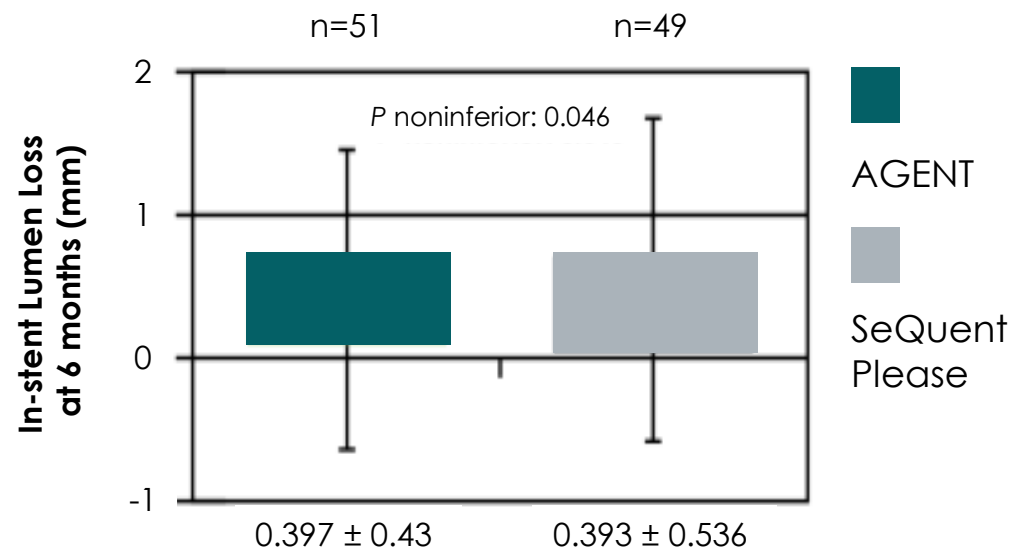
AGENT™ In-stent Restenosis (ISR) Clinical Study

First Head-to-Head Study of Two DCBs

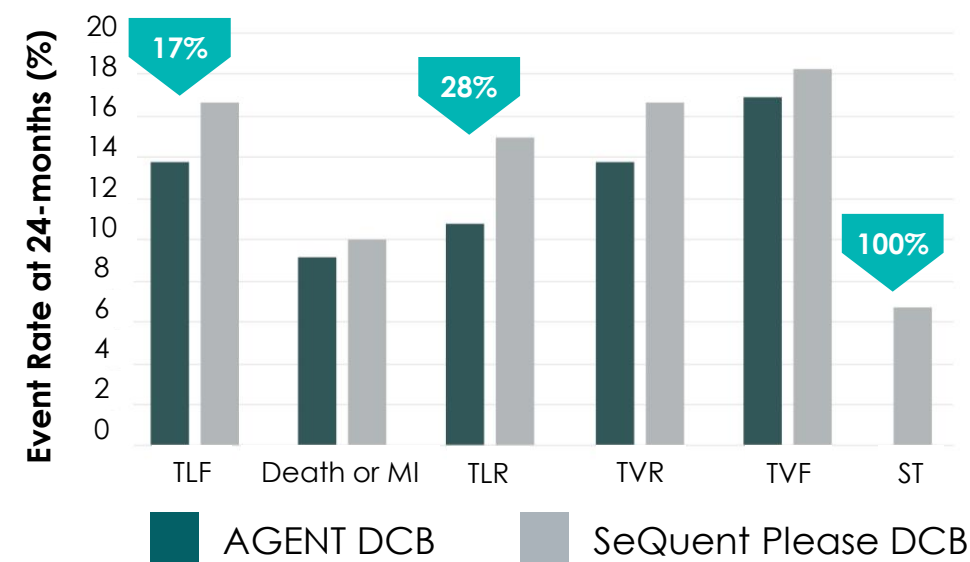
Primary endpoint met and non-inferiority achieved despite lower balloon drug load

Balloon Drug Load: AGENT™: 2 µg/mm², SeQuent Please™: 3 µg/mm²

Primarily Endpoint Late Lumen Loss (LLL) at 6 months



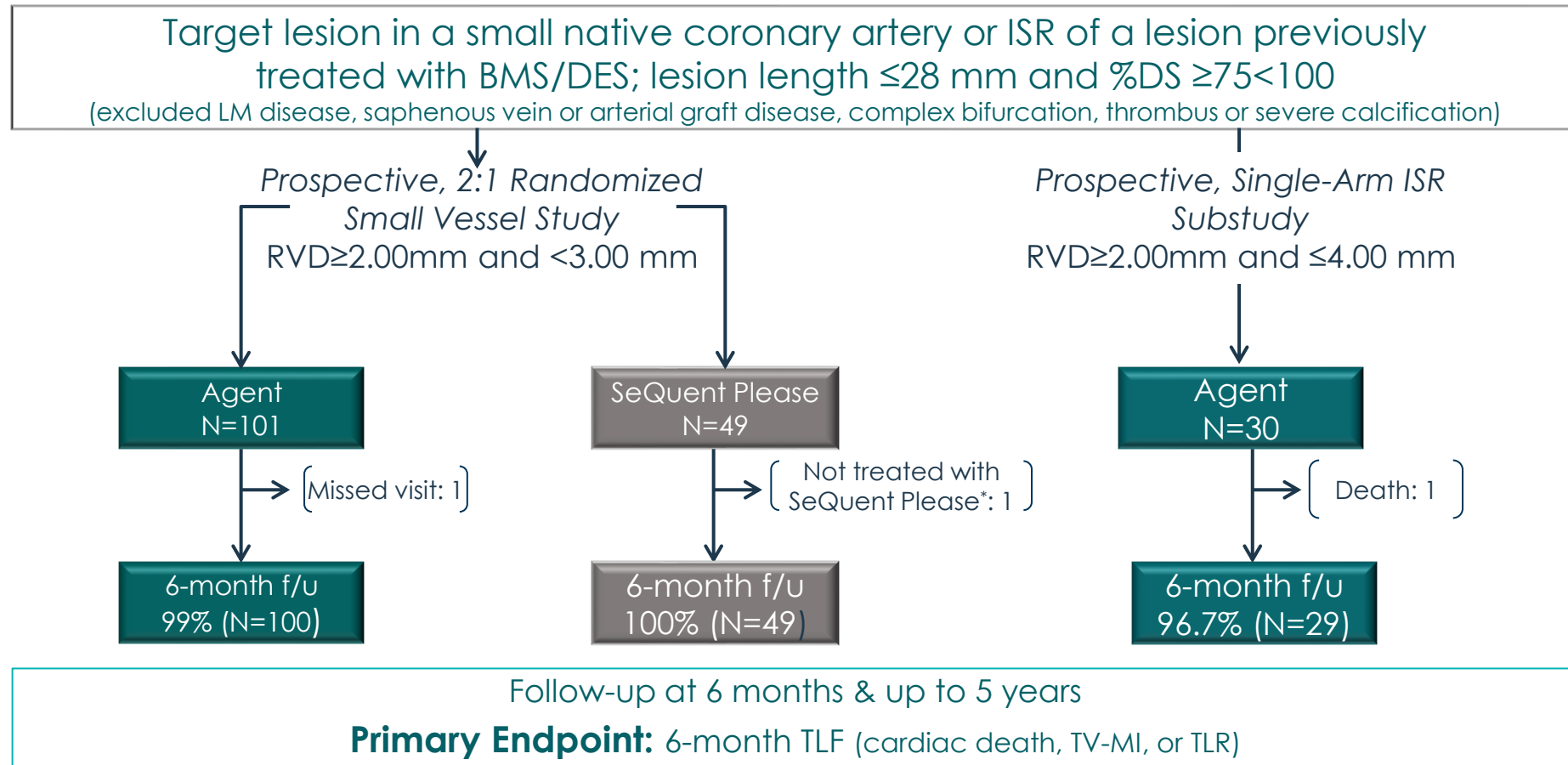
Numerically Lower 24-month Event Rates





AGENT™ Japan Small Vessel Study Trial Design

A multicenter, prospective, 2:1 randomized, non-inferiority study comparing Agent™ vs. SeQuent Please™ DCB in small vessel de novo lesions



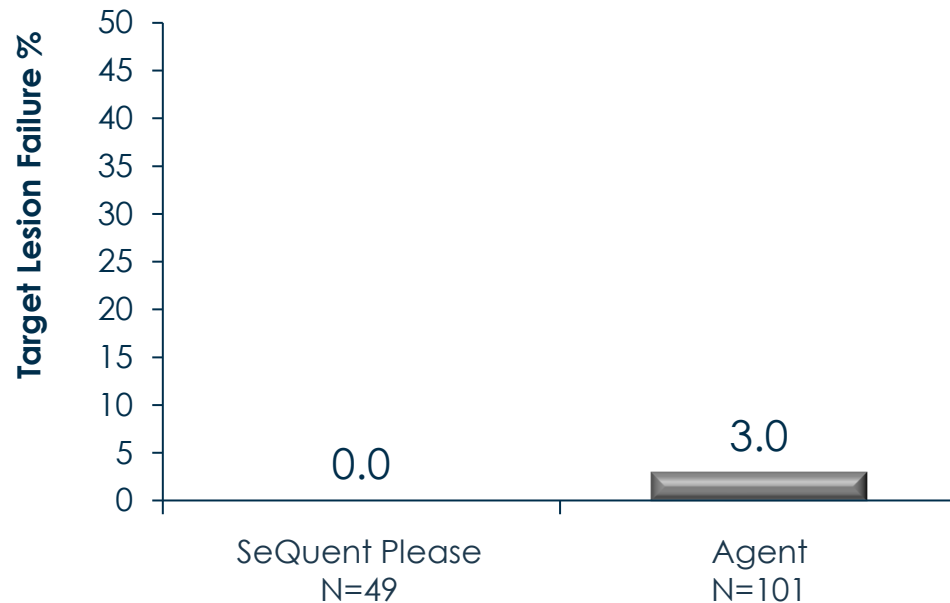
AGENT™ Japan Small Vessel (SV) Study

First Head-to-Head DCB SV Study

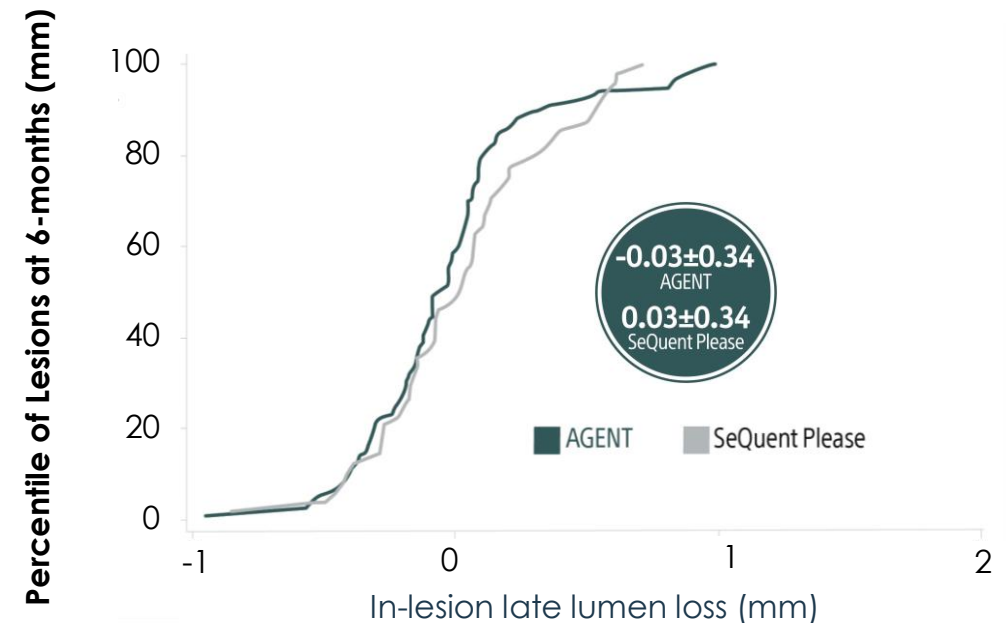
Primary endpoint met and non-inferiority achieved despite lower balloon drug load

Balloon Drug Load: AGENT™: 2 µg/mm², SeQuent Please™: 3 µg/mm²

Primary Endpoint TLF at 6 Months



Similarly Low Levels of Late Lumen Loss

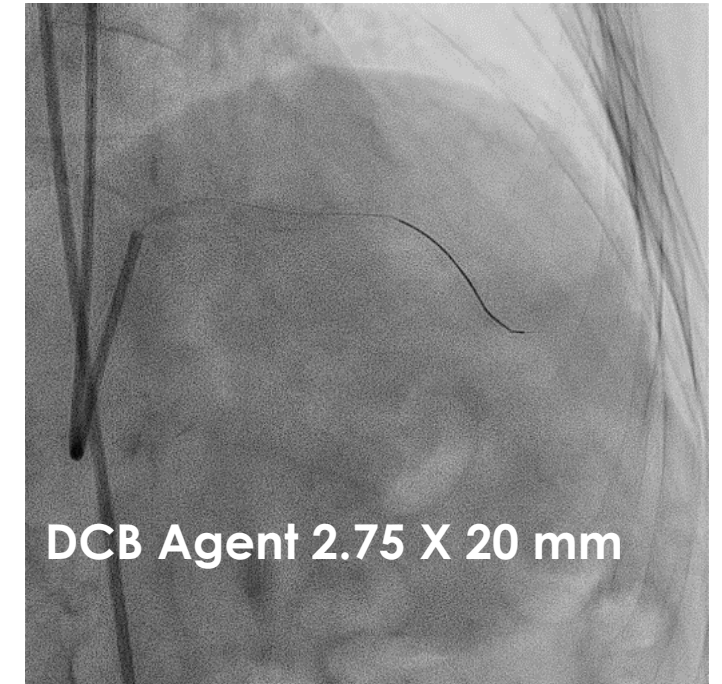
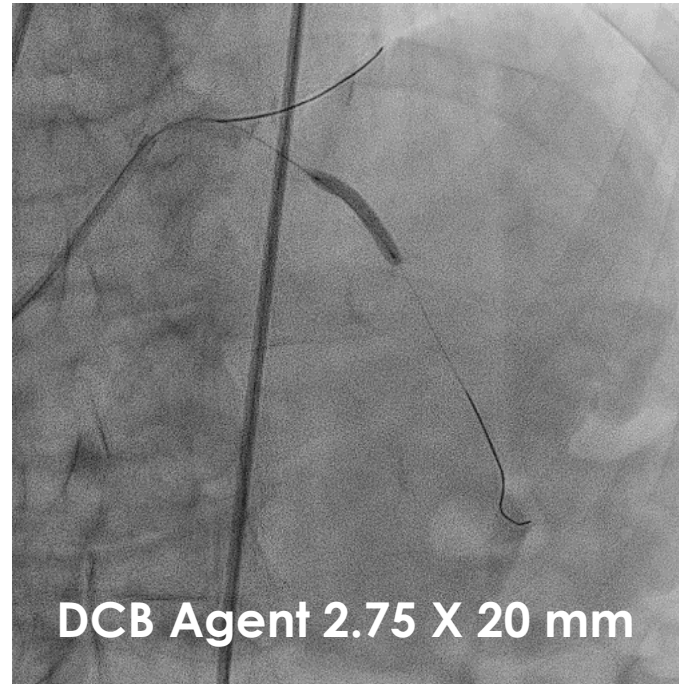
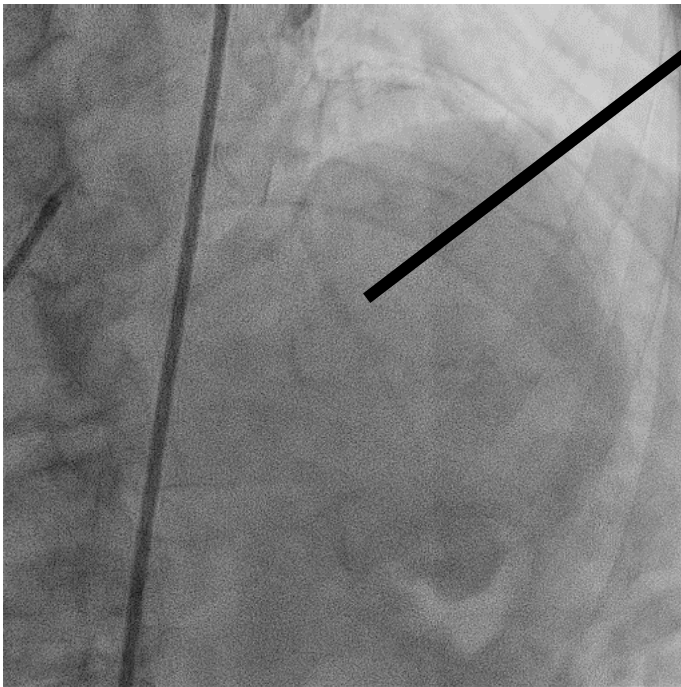


F/91 NSTEMI, HTN, DM, A.fib with NOAC

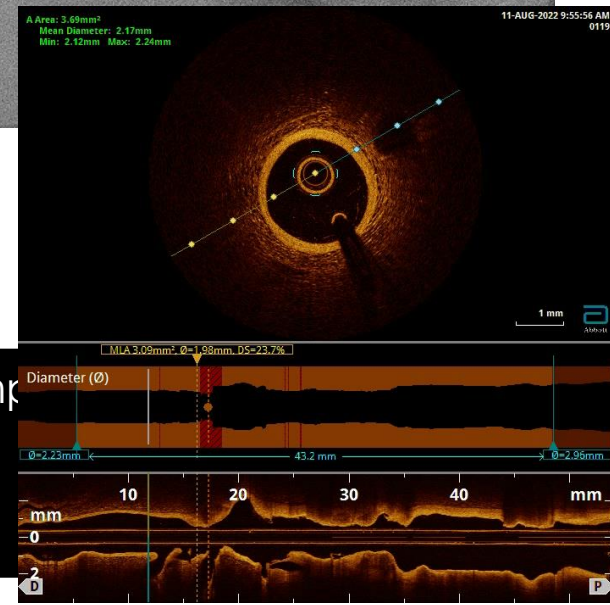
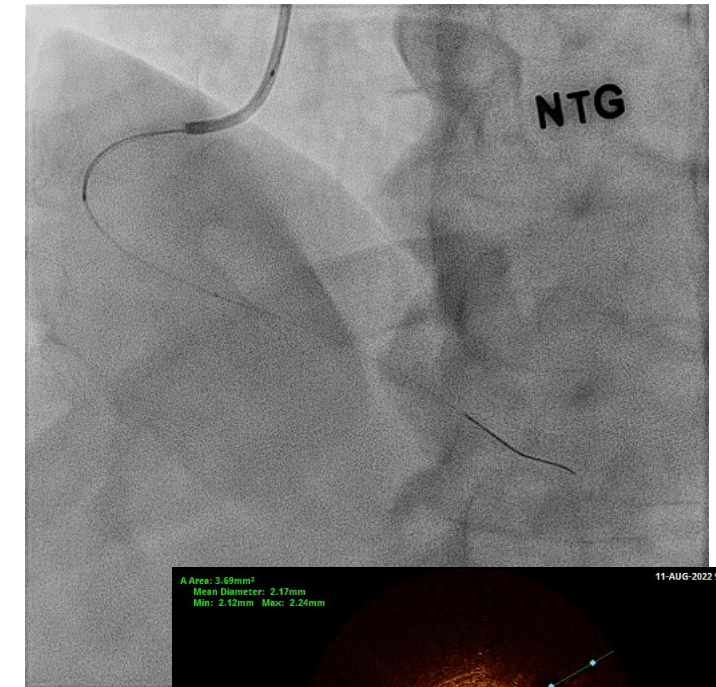
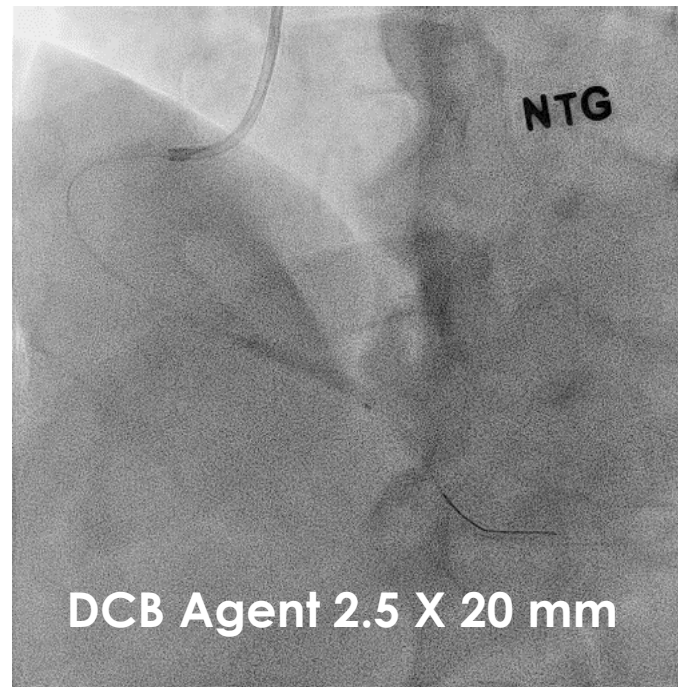
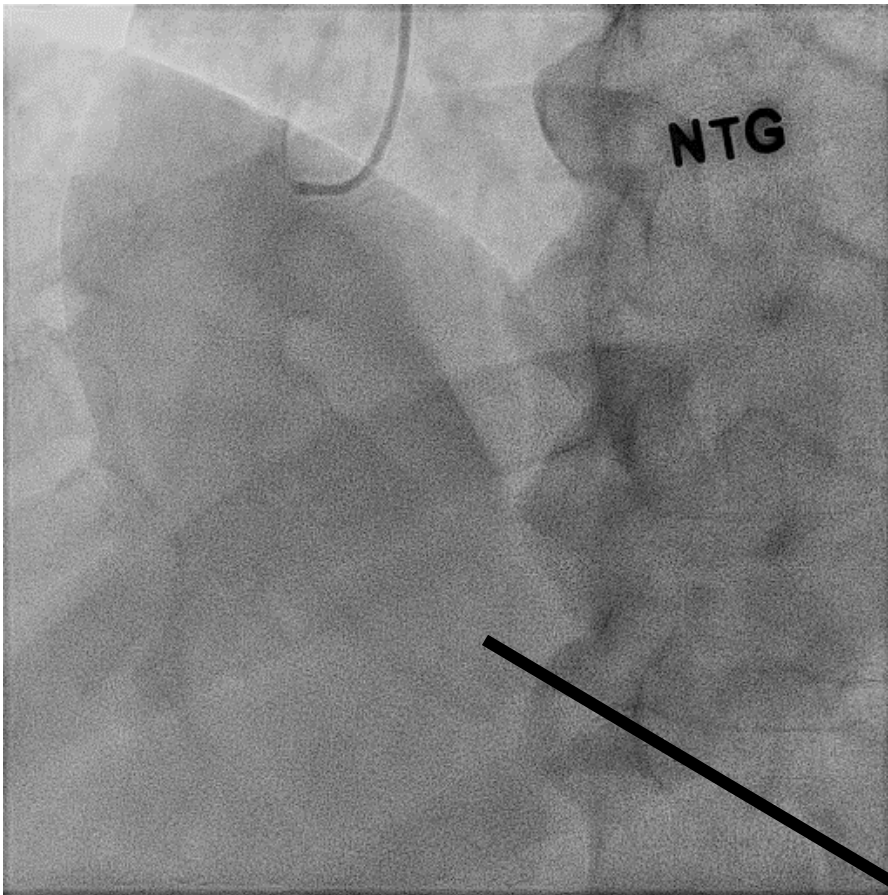
This bifurcated lesion, frail very old women with anticoagulation! What is your plan?

1. Just balloon angioplasty ?
2. Implant metal stent?
3. How about balloon angioplasty and drug delivery ?

→ **Drug coated balloon with side branch patency, shorter DAPT, no stent related issue**



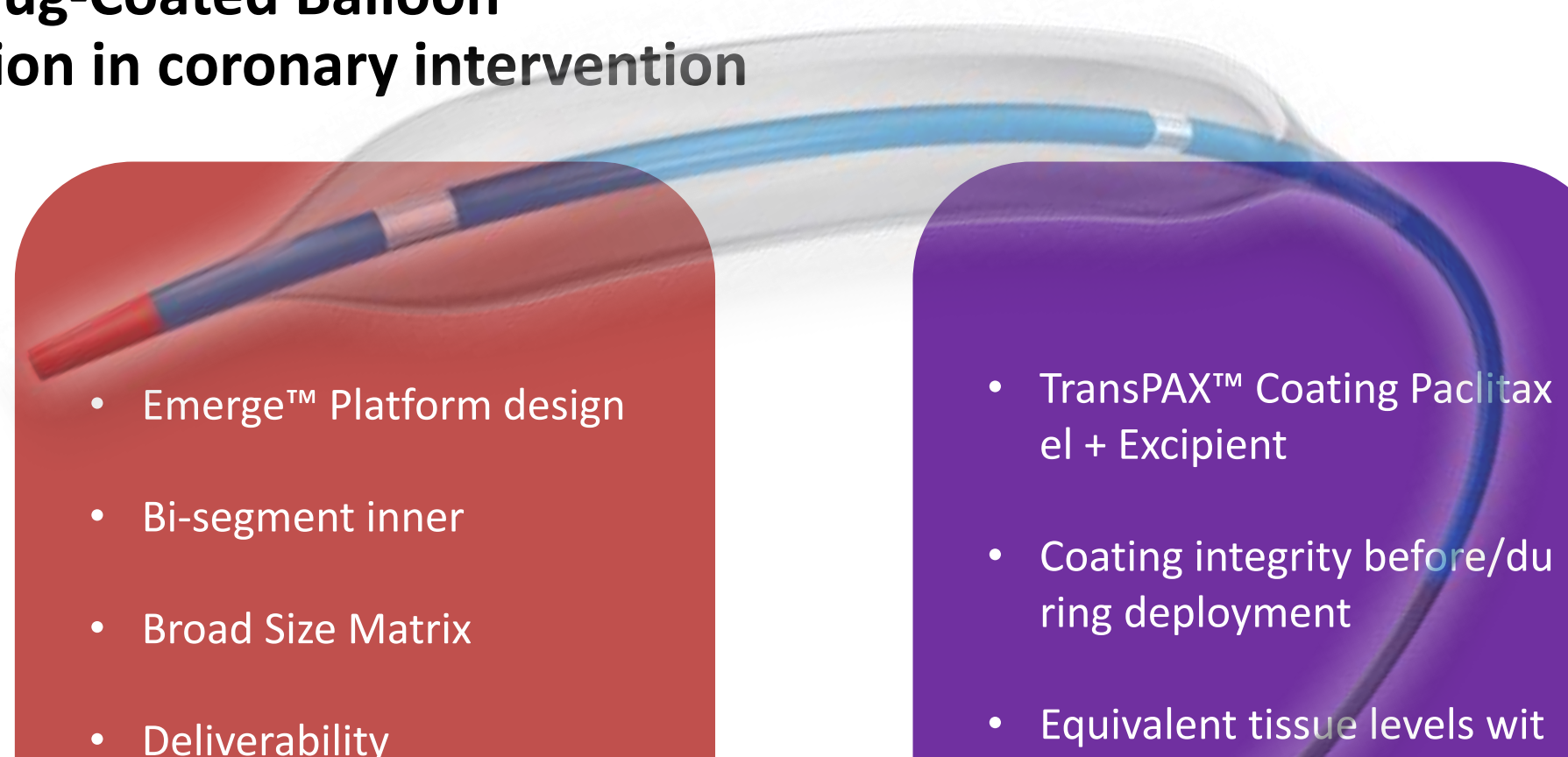
M/58 Unstable angina, HTN



Bifurcated lesion and both main and side branch size compromised. What is your choice?

1. **Metal stent with side branch compromise?**
2. **Drug coated balloon with nothing behind?**

Agent™ Drug-Coated Balloon : new option in coronary intervention

- 
- Emerge™ Platform design
 - Bi-segment inner
 - Broad Size Matrix
 - Deliverability

- TransPAX™ Coating Paclitaxel + Excipient
- Coating integrity before/during deployment
- Equivalent tissue levels with less drug load than other DCBs

- Agent combines the exceptional deliverability of the Emerge™ platform with the efficient drug transfer technology of TransPax™ coating.
- Agent would be the new option for ISR and small vessel coronary disease

Thank you for attention



CHUNG-ANG UNIVERSITY
GWANG-MYEONG HOSPITAL