Cook Incorporated
Zilver PTX Drug-Eluting Stent
FDA Review of P100022

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FDA Presentations

- Allison Kumar
  Introduction
- Dr. Steven Brooks
  Zilver PTX Study design, clinical results and consideration
- Dr. Cindy Yang
  Zilver PTX Study statistical conclusions and recommendations
- Dr. George Aggrey
  Post-approval study considerations
- Allison Kumar
  Conclusions

Introduction Outline

- Indications for Use
- Key Regulatory Milestones
- Device Description
- Pre-Clinical Testing
- Discussion Points

Proposed Indications

The Zilver PTX Drug-Eluting Stent is indicated for improving luminal diameter for the treatment of *de novo* or restenotic symptomatic lesions in vascular disease of the above-the-knee femoropopliteal arteries having reference vessel diameter from 4 mm to 9 mm and total lesion lengths up to 140 mm per limb and 280 mm per patient. To avoid involvement of the common femoral artery, the most proximal stent end should be placed at least 1 cm below the origin of the superficial femoral artery. To avoid involvement of the below-the-knee popliteal artery, the most distal stent end should be placed above the plane of the femoral epicondyles.

P100022
Key Regulatory Milestones

June 2004

- FDA conditionally approved an Investigational Device Exemption (IDE) for the Zilver PTX study (G030251)
  - Allowed enrollment of U.S. subjects into phase I of the study.
  - Phase I subjects had lesion lengths <7 cm, and could only receive a single Zilver PTX stent.

April 2006

- Enrollment of registry subjects began.
  - Subjects were from Europe, Canada, and South Korea.
  - Enrollment concluded in June 2008.

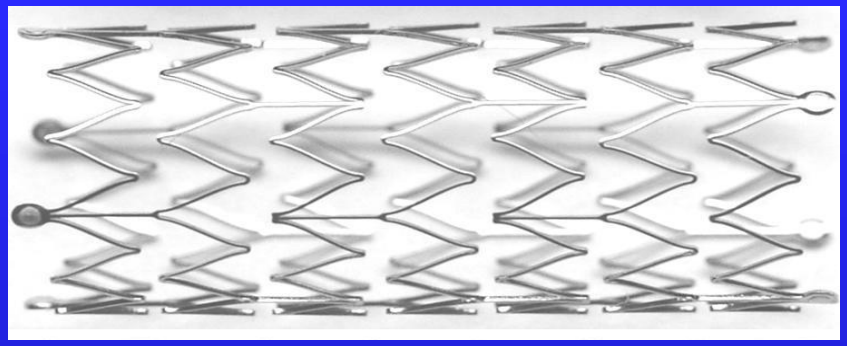
August 2007

- FDA fully approved IDE, based on safety data provided by the sponsor.
  - Allowed enrollment of subjects into Phase 2 of study.
  - Phase 2 consisted of patients with lesion length 0 – 14 cm.

June 2010

- FDA filed PMA (P100022)
  - The subject of this advisory panel meeting
  - Includes the agreed-upon analysis of the full pivotal study cohort of 479 subjects from the Zilver PTX study and the registry study cohort of 787 international subjects

Device Description



- The Cook Zilver PTX Drug-Eluting Stent
  - Nitinol stent coated with the drug paclitaxel at a dose density of 3µg/mm^2
    - No polymer, binder, or excipient
    - Paclitaxel is the same API used in some currently approved coronary drug-eluting stents.
  - Size matrix: 5 – 10 mm in diameter and 20 – 80 mm in length
- Stent is preloaded on a 6 Fr delivery system.
  - Delivery system is identical to the approved Zilver Vascular Stent (P080017), indicated for use in the iliac arteries.

Pre-Clinical Review

- Stent Functional Testing
- Stent Coating Testing
- Stent Delivery System Testing
- Animal Studies
- Chemistry, Manufacturing, & Controls (CMC)
- Sterilization & Packaging
- Biocompatibility
- Manufacturing (QS/GMP)

Review of Drug Studies Safety Data

- Information referenced and contained within the Drug Master File (DMF).
  - Safety Pharmacology
  - Toxicity
- Pharmacokinetic (PK) testing
  - Local drug tissue levels seen to much higher than concentration of paclitaxel needed for antiproliferative effects
  - Tissue levels reduced, but remained high through 2 months
  - Concerns related to toxicity and prolonged retention time were mitigated by animal and clinical studies

Primary Discussion Points

- Appropriateness of Indication
- Medical Therapy
- Effects of Bail Out Stenting
- Long Term Follow-Up
- Stent Fracture
- Overall Safety and Effectiveness
- Post-approval Study Considerations

FDA Presentations

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Cook Incorporated Zilver PTX Drug-Eluting Stent

FDA Review of P100022

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Medical Officer

Division of Cardiovascular Devices

Office of Device Evaluation

Food and Drug Administration

Presentation Outline

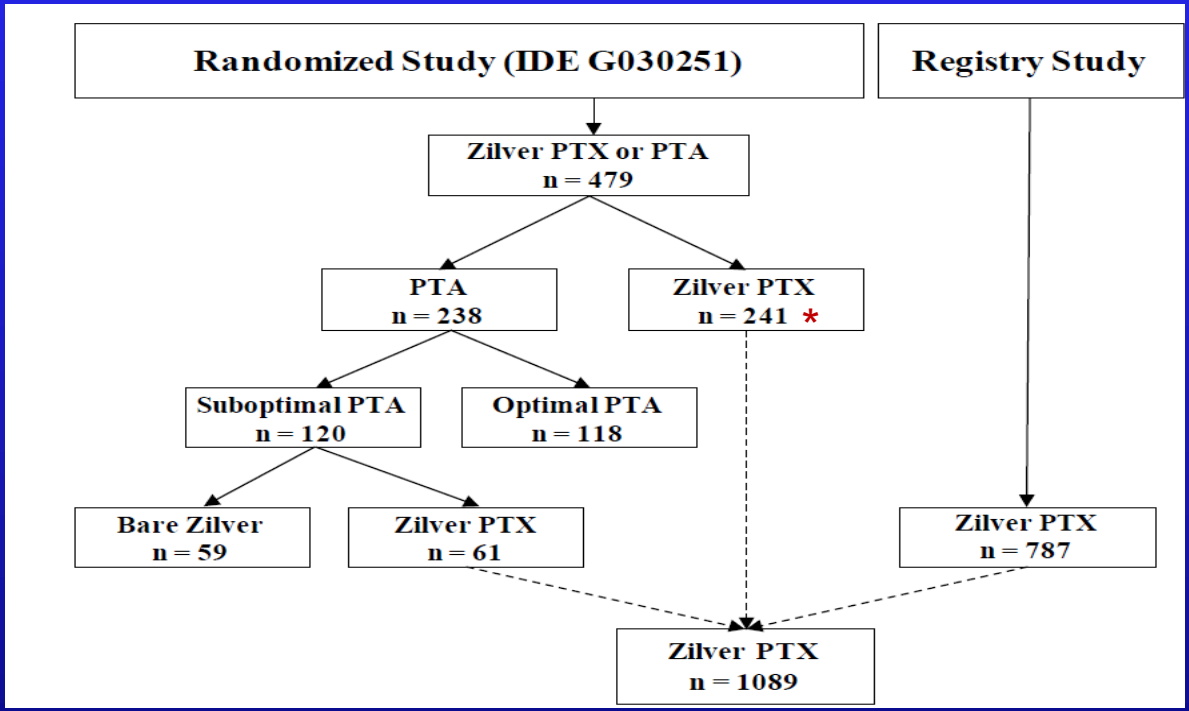
- Summary of Clinical Testing
- Randomized Clinical Trial
  - Principal Inclusion/Exclusion Criteria
  - Patient Demographics
  - Primary Safety Endpoint
  - Primary and Secondary Effectiveness Endpoints
  - Additional Analyses
  - Substudies
- Registry Study
- Overall Interpretation of Safety and Effectiveness
- Clinical Conclusions

Cook Incorporated Zilver PTX Drug-Eluting Stent

Summary of the Clinical Testing

Clinical Evaluation Strategy

- Randomized Control Trial (RCT) under IDE G030251
- Global Registry



* Includes 5 live case patients

Zilver PTX Randomized Controlled Trial

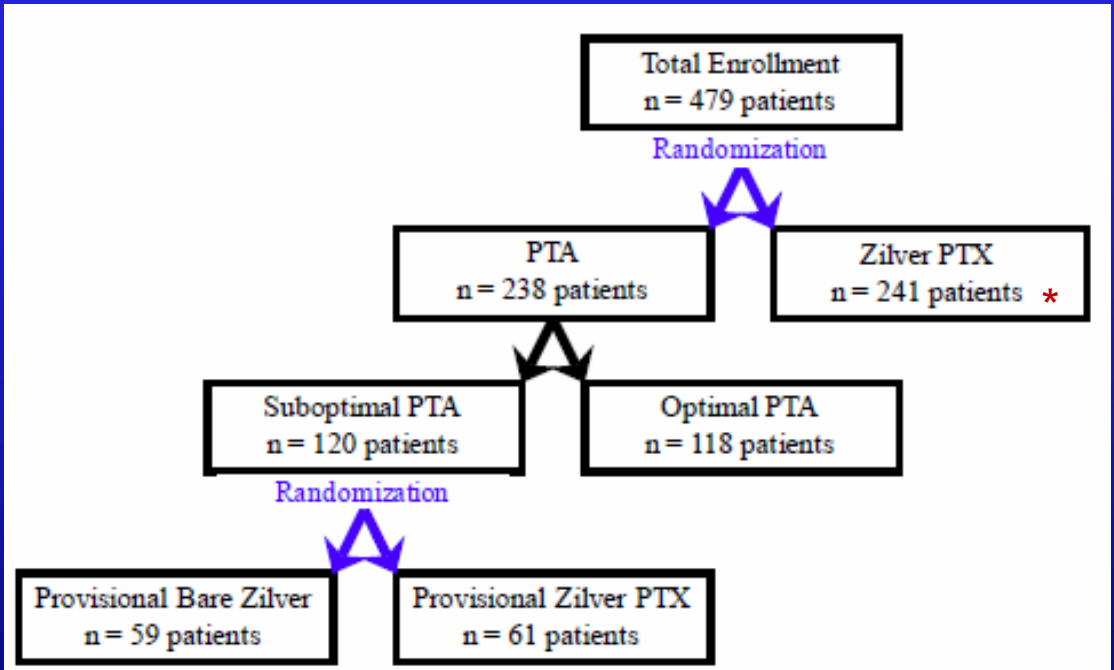
(IDE G030251)

Purpose

- To demonstrate non-inferior safety and superior effectiveness of the Zilver PTX stent to PTA for treatment of *de novo* or restenotic lesions of the above the knee femoropopliteal artery

Trial Design

- Prospective, controlled, open label
- Multicenter (US, Japan, Germany)
- Randomization 1:1 Zilver PTX or PTA
  - Suboptimal PTA: 2° 1:1 Randomization: Zilver PTX or bare Zilver stent



Inclusion Criteria - Overview

- Up to 2 stenotic or occluded atherosclerotic lesions (≤ 14 cm long, or ≤ 7 cm for the first 60 subjects enrolled) of the above-the-knee femoropopliteal artery, up to one in each limb.
- Reference vessel diameter of 4 - 9 mm.
- *De novo* or restenotic lesion(s) with > 50% stenosis documented angiographically and no prior stent in the target lesion.
- Symptoms of peripheral arterial disease classified as Rutherford Category 2 or greater.
- Patient has a resting ABI < 0.9 or an abnormal exercise ABI if resting ABI is normal. Patient with incompressible arteries (ABI > 1.2) must have a TBI < 0.8.

Exclusion Criteria - Overview

- Significant stenosis (> 50%) or occlusion of inflow tract not successfully treated before this procedure to a < 30% residual stenosis.
- Patient has undergone an unsuccessful arterial interventional treatment of the legs within 30 days prior to the study procedure.
- Patient has a planned procedure involving arterial interventional treatment of the study leg(s) within the 12-month follow-up period.
- Patient has had previous stenting of the target vessel.
- Patient lacks at least one patent vessel of runoff with < 50% stenosis throughout its course.
- Patient has untreated angiographically-evident thrombus in the target lesion.
- Patient has a bypass graft with an anastomosis in the target vessel.
- Patient has lesions requiring atherectomy (or ablative devices), cutting balloons, cryoplasty balloons, or any other advanced device to facilitate stent delivery.

Primary Safety Endpoint

Safety – 12 Month Event Free Survival

- 12-month event-free survival (EFS) - freedom from CEC-adjudicated Major Adverse Events
  - Death
  - Target Lesion Revascularization (TLR)
  - target limb ischemia requiring surgical intervention or surgical repair of the target vessel
  - freedom from worsening Rutherford classification by 2 classes or to class 5 or 6.

Primary Analysis:

- Per-protocol analysis
- Per-patient basis
- Non-inferiority of EFS of Zilver PTX to PTA
- Non-inferiority margin of 10%.

Primary Effectiveness Endpoint

Effectiveness – 12 Month Primary Patency:

- Open treated segment with < 50% diameter stenosis
- Assessed via duplex ultrasound (PSV < 2.0) and/or angiography.

Primary Analysis:

- Intent-to-treat population
- Per-lesion basis
- Superiority comparison

Secondary Endpoints

- procedural success
- 12-month clinical success based on an improvement of 2 Rutherford categories
- 12-month clinical improvement based on an improvement of 1 Rutherford category
- 12-month secondary patency
- 12-month restenosis rate
- 12-month thrombosis rate
- 12-month functional status improvement as measured by ABI and the Walking Impairment Questionnaire

Patient Enrollment

- 55 Sites in US, Germany and Japan
- 479 Subjects (81.4% US)
- 236 Randomized to Zilver PTX (+5 live cases)
- 238 Randomized to PTA (control) group
  - 118 Optimal PTA
  - 120 Bailout Stenting
    - 59 Bare Zilver
    - 61 Zilver PTX

Patient Demographics

Demographic	Control Group	Treatment Group	Diff. (95% CI)	P-Value
Age	67.7 ± 10.6 (238)	67.9 ± 9.6 (236)	-.1 (-2.0, 1.7)	0.88
Gender				
Male	63.9% (152/238)	65.7% (155/236)	-1.8 (-10.4, 6.8)	0.70
Female	36.1% (86/238)	34.3% (81/236)	1.8 (-6.8, 10.4)	
Ethnicity				
Asian	14.1% (29/206)	11.9% (25/210)	2.2 (-4.3, 8.6)	
Black/African American	11.2% (23/206)	11.9% (25/210)	-0.7 (-6.9, 5.4)	0.81
Hispanic/Latino	5.3% (11/206)	7.1% (15/210)	-1.8 (-6.5, 2.8)	
White/Caucasian	69.4% (143/206)	69.0% (145/210)	0.4 (-8.5, 9.2)	
Height	66.4 ± 4.4 (238)	66.7 ± 3.6 (236)	-0.2 (-1.0, 0.5)	0.55
Weight	178.5 ± 44.3 (238)	180.4 ± 40.0 (236)	-1.9 (-9.5, 5.8)	0.62
Body Mass Index	28.2 ± 5.6 (238)	28.4 ± 5.3 (236)	-0.2 (-1.2, 0.8)	0.71

Medical History

	Control Group	Treatment Group	Diff. (95% CI)	P-Value
Diabetes	42.0% (100/238)	49.6% (117/236)	-7.6 (-16.5, 1.4)	0.11
Hypercholesterolemia	69.7% (166/218)	76.3% (180/236)	-6.5 (-14.5, 1.5)	0.12
Hypertension	81.5% (194/238)	89.0% (210/236)	-7.5 (-13.8, -1.1)	0.02*
Pulmonary Disease	16.0% (38/238)	19.1% (45/236)	-3.1 (-9.9, 3.7)	0.39
Previous MI	17.2% (41/238)	21.2% (50/236)	-4.0 (-11.0, 3.1)	0.29
Smoking Status				
Never Smoked	15.5% (37/238)	13.6% (32/236)	2.0 (-4.4, 8.3)	
Quit	51.7% (123/238)	55.5% (131/236)	-3.8 (-12.8, 5.1)	0.70
Still Smokes	32.4% (77/238)	30.9% (73/236)	1.4 (-7.0, 9.8)	

*Statistically Significant, with no adjustment of multiplicity

Select Lesion Characteristics

Characteristics		Control Group	Treatment Group	Diff. (95% CI)	P-Value
Lesion Class (TASC)	A	36.0% (86/239)	29.4% (69/235)	6.6 (-1.8, 15.04)	0.07
	B	25.9% (62/239)	22.6% (53/235)	3.4 (-4.3, 11.1)	
	C	31.0% (74/239)	42.6% (100/235)	-11.6 (-20.2, -3.0)	
	D	7.1% (17/239)	5.5% (13/235)	1.6 (-2.8, 6.0)	
Calcification	None	4.8% (12/249)	1.7% (4/241)	3.2 (0.05, 6.3)	< 0.01*
	Little	38.2% (95/249)	25.7% (62/241)	12.4 (4.3, 20.6)	
	Moderate	22.1% (55/249)	35.3% (85/241)	-13.2 (-21.1, -5.3)	
	Severe	34.9% (87/249)	37.3% (90/241)	-2.4 (-10.9, 6.1)	
Inflow Tract Stenosis	None	41.6% (96/231)	37.1% (76/205)	4.5 (-4.7, 13.7)	0.03*
	≤ 50%	45.5% (105/231)	40.5% (83/205)	5.0 (-4.3, 14.3)	
	> 50%	13.0% (30/231)	22.4% (46/205)	-9.5 (-16.6, -2.3)	

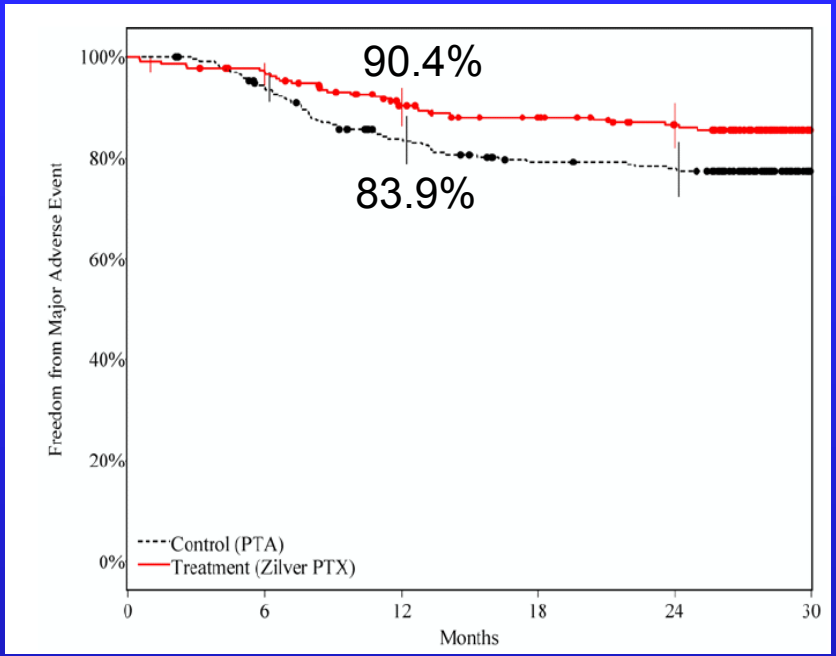
*Statistically Significant, with no adjustment of multiplicity

Primary Safety Analysis

	Per Protocol (PP)
Zilver PTX Treatment Group	90.4% (86.3%, 93.9%)
PTA Control Group	83.9% (79.0%, 88.4%)

- **Per Protocol Analysis**
- **Kaplan-Meier estimate and 95% confidence intervals for 12-month event-free survival**

Primary Safety Endpoint Analysis



Months Post-procedure	Event-free Survival Estimate		Standard Error		Cumulative Failed		Cumulative Censored		Number Remaining	
	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)
0	100.0%	100.0%	0.0%	0.0%	0	0	0	0	236	235
1	100.0%	99.1%	0.0%	0.6%	0	2	0	0	236	233
6	94.4%	97.0%	1.5%	1.1%	13	7	6	3	217	225
12	83.9%	90.4%	2.4%	1.9%	37	22	15	16	184	197
24	77.9%	86.6%	2.8%	2.3%	50	30	22	33	164	172

Major Adverse Events
(12 months)

Individual MAE	Control (PTA)	Treatment (PTX)
Clinically Driven TLR	16.3% (36/221)	9.6% (21/219)
Worsening Rutherford	0.9% (2/221)	0.0% (0/219)
Amputation	0.0% (0/221)	0.5% (1/219)
Death *	0.0% (0/221)	0.0% (0/219)
All Cause Mortality	1.8% (4/221)	4.1% (9/219)

* CEC Adjudicated Death

Stent Thrombosis*

	0 - 12 Months	0 - 24 Months
Bare Zilver	3.6%	3.6%
Zilver PTX treatment group	2.5%	2.9%
All Zilver PTX (AT Group)	2.0%	2.3%

- All events except 3 from Zilver PTX group occurred while on antiplatelet therapy

•KM estimates

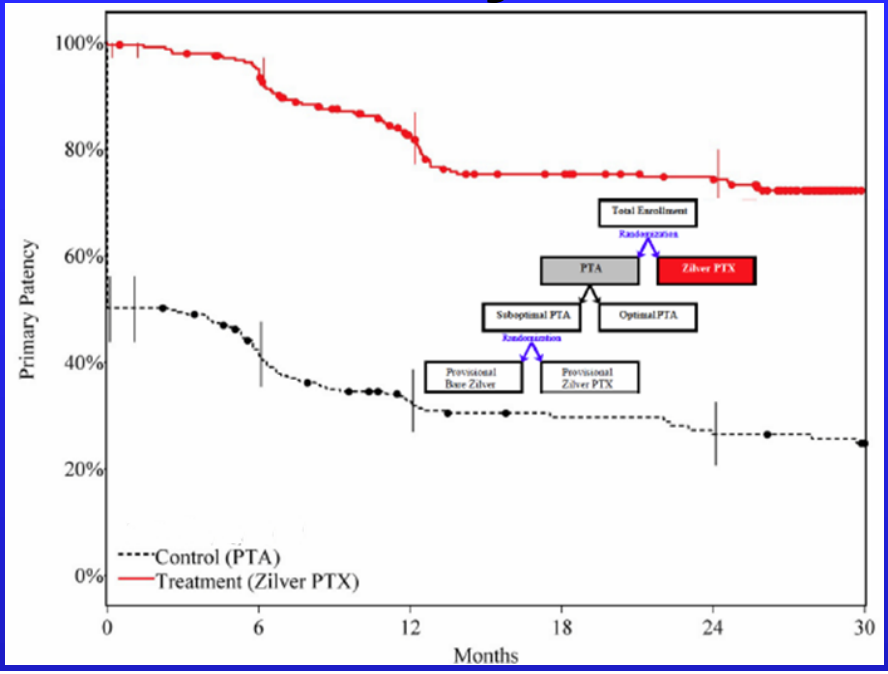
Primary Effectiveness Endpoint Analysis – 12 Month Primary Patency

	Intention-to-treat (ITT)
Zilver PTX Treatment Group	75.9% (69.9%, 81.1%)
PTA Control Group	28.2% (22.7%, 34.3%)

- GEE model
- ITT population
- $p < 0.01$

Primary Effectiveness Endpoint Analysis*

*KM Analysis
*ITT Population



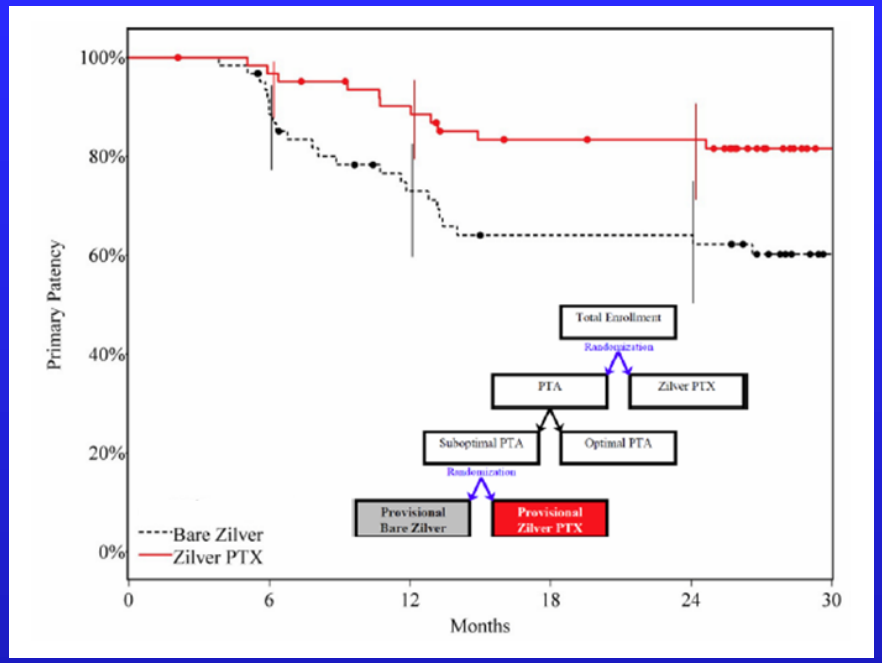
Months Post-procedure	Primary Patency Estimate		Standard Error		Cumulative Failed		Cumulative Censored		Number Remaining	
	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)
0	50.2%	99.6%	3.2%	0.4%	125	1	0	0	126	245
1	50.2%	99.6%	3.2%	0.4%	125	1	0	1	126	244
6	41.6%	95.1%	3.1%	1.4%	146	12	5	4	100	230
12	32.7%	82.7%	3.0%	2.5%	167	41	11	23	73	182
24	26.5%	74.8%	3.1%	2.9%	177	58	41	39	33	149

Secondary Effectiveness Endpoints

	Control (PTA)	Treatment (PTX)
Procedural Success	57.3%	95.0%
12-month Clinical Success	57.8%	54.9%
12-month Clinical Improvement	77.7%	76.2%
12-month Secondary Patency	98.5%	98.2%
12-month Restenosis Rate	26.5%	17.3%
12-month Thrombosis Rate	n/a	2.0%
ABI - Change at 12-months	21.0%	24.0%

*KM Estimates

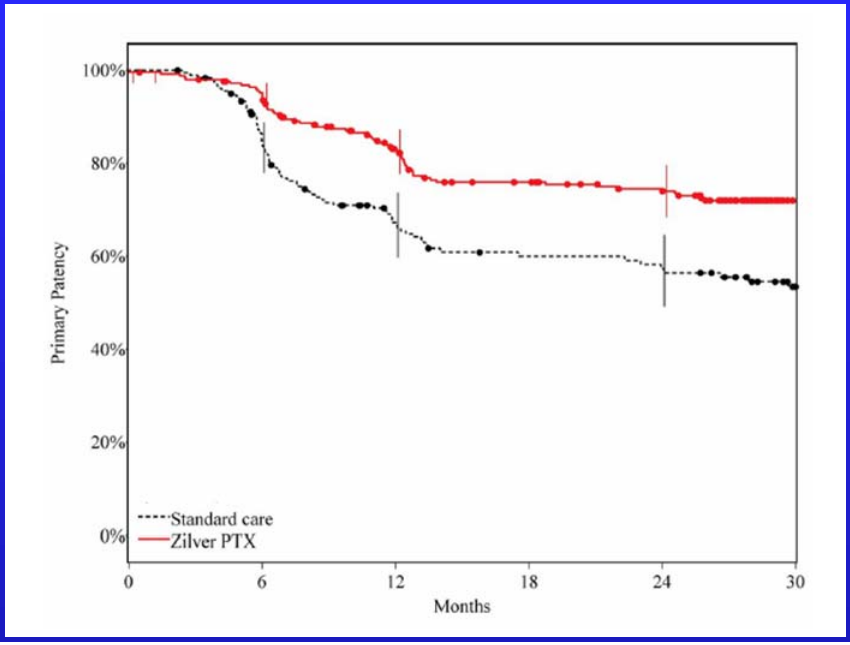
Patency of Provisional Bare Zilver vs. Provisional Zilver PTX



Months Post-procedure	Primary Patency Estimate		Standard Error		Cumulative Failed		Cumulative Censored		Number Remaining	
	Bare Zilver	Zilver PTX	Bare Zilver	Zilver PTX	Bare Zilver	Zilver PTX	Bare Zilver	Zilver PTX	Bare Zilver	Zilver PTX
Intent-to-treat										
0	100.0%	100.0%	0.0%	0.0%	0	0	0	0	62	63
1	100.0%	100.0%	0.0%	0.0%	0	0	0	0	62	63
6	88.4%	96.8%	4.1%	2.2%	7	2	2	1	53	60
12	72.9%	90.2%	5.8%	3.8%	16	6	5	3	41	54
24	64.1%	83.4%	6.3%	4.8%	21	10	6	7	35	46

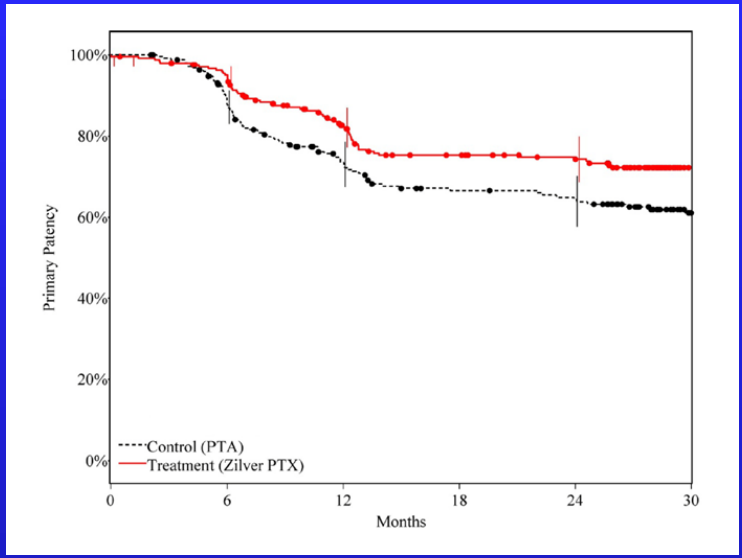
Patency of Primary Zilver PTX vs. Standard Therapy

(Optimal PTA + Provisional Bare Metal Zilver)



Months Post-procedure	Primary Patency Estimate		Standard Error		Cumulative Failed		Cumulative Censored		Number Remaining	
	Standard Care	Zilver PTX	Standard Care	Zilver PTX	Standard Care	Zilver PTX	Standard Care	Zilver PTX	Standard Care	Zilver PTX
Standard Care vs. Primary Zilver PTX										
0	100.0%	99.6%	0.0%	0.4%	0	1	0	0	182	251
1	100.0%	99.6%	0.0%	0.4%	0	1	0	1	182	250
6	84.2%	95.2%	2.7%	1.4%	28	12	7	4	147	236
12	67.3%	83.1%	3.6%	2.4%	57	41	16	23	109	188
24	57.3%	74.5%	3.9%	2.9%	71	60	46	39	65	153

Primary Zilver PTX vs. Optimal PTA + Provisional Bare Zilver + Provisional Zilver PTX



Months Post-procedure	Primary Patency Estimate		Standard Error		Cumulative Failed		Cumulative Censored		Number Remaining	
	PTA + Bare Zilver + Zilver PTX	Primary Zilver PTX	PTA + Bare Zilver + Zilver PTX	Primary Zilver PTX	PTA + Bare Zilver + Zilver PTX	Primary Zilver PTX	PTA + Bare Zilver + Zilver PTX	Primary Zilver PTX	PTA + Bare Zilver + Zilver PTX	Primary Zilver PTX
Intent-to-treat										
0	100.0%	99.6%	0.0%	0.4%	0	1	0	0	251	245
1	100.0%	99.6%	0.0%	0.4%	0	1	0	1	251	244
6	87.8%	95.1%	2.1%	1.4%	30	12	8	4	213	230
12	73.5%	82.7%	2.8%	2.5%	64	41	19	23	168	182
24	64.3%	74.8%	3.2%	2.9%	83	58	54	39	114	149

Pharmacokinetic (PK) Substudy

- 60 subjects in PK Substudy
- Blood draws at 3 of 11 timepoints up to 12hrs
- Minimal paclitaxel delivered systemically - (C_{max} < 10 ng/mL)
- <1 ng/mL detected in plasma at 8 & 12 hrs

- Conclusion: Rapid paclitaxel elution and low plasma drug levels

Angiographic/IVUS Substudy

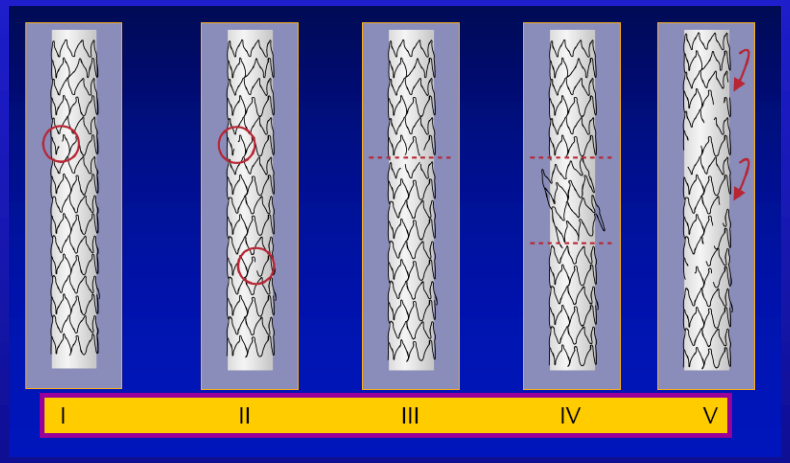
- 40 Patients each from Treatment/Control Groups
- Good correlation between ultrasound and angiographic patency results
- 2 instances of stent malapposition 2/85 (2.4%)
- 0 instances of stent malapposition at 6 & 12 mo

12 Month Stent Integrity

12 Month Stent Fracture Incidence	
Imaging Timepoint	**Fracture Rate**
Pre-Discharge	0.0% (0/528)
12 Months	0.9% (4/457)

Stent Fracture Classification:

I. Single strut only
II. Multiple single stent fractures occurring at different sites
III. Multiple single strut fractures resulting in complete transverse fracture but without stent displacement
IV. Complete transverse linear fracture with stent displacement
V. Spiral fracture



*Allie, Hebert, and Walker (2004)

RCT Conclusions

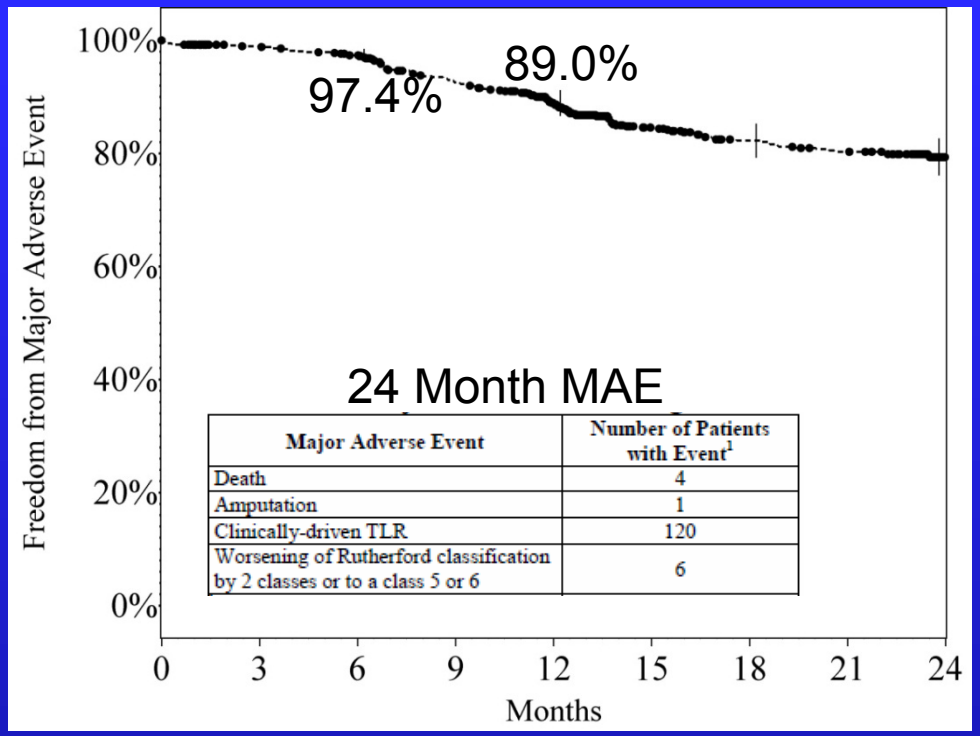
- Zilver PTX RCT met pre-specified safety and effectiveness primary endpoints
- Results of the control arm are consistent with literature derived values
- There was no safety signal of elevated rates of death, stent thrombosis, or stent fracture
- Due to sample size of 479, limited conclusions can be drawn for rare clinical events

Zilver PTX Global Registry

Registry Design

- Non-randomized, open label, observational
- Prospectively enrolled 787 consecutive patients
- Multicenter (30 Centers-Europe, Canada, Korea)
- De novo or restenotic above-the-knee femoropopliteal artery
- No limit on lesion length
- Follow-up to 2 years
- Patient selection criteria similar to RCT except:
  - Up to 4 overlapping Zilver PTX stents
  - If >4 stents necessary, Bare Zilver to be used
  - EF 25-35% and NYHA Class III eligible

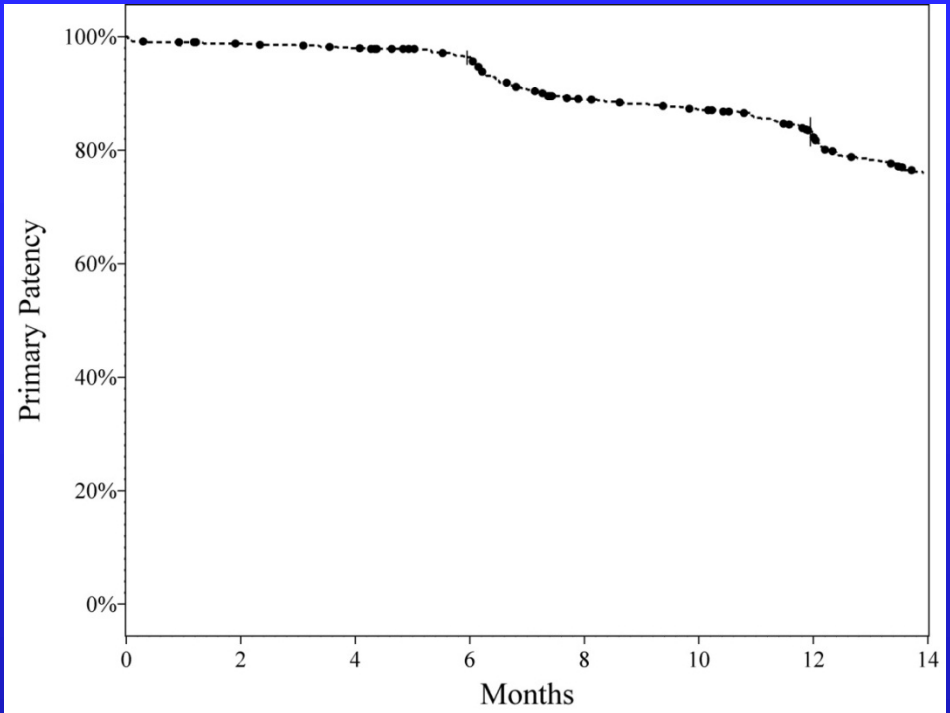
Results: Event Free Survival



Major Adverse Event	Number of Patients with Event[1]
Death	4
Amputation	1
Clinically-driven TLR	120
Worsening of Rutherford classification by 2 classes or to a class 5 or 6	6

Months Post-procedure	Estimate	Standard Error	Cumulative Number Failed	Cumulative Number Censored	Number Remaining
0	100.0%	0%	0	6	781
1	99.2%	0.3%	6	13	768
6	97.4%	0.6%	20	42	725
12	89.0%	1.2%	80	143	564
18	82.3%	1.5%	115	292	380
24	79.3%	1.7%	128	419	240

Results: 12 mo Patency

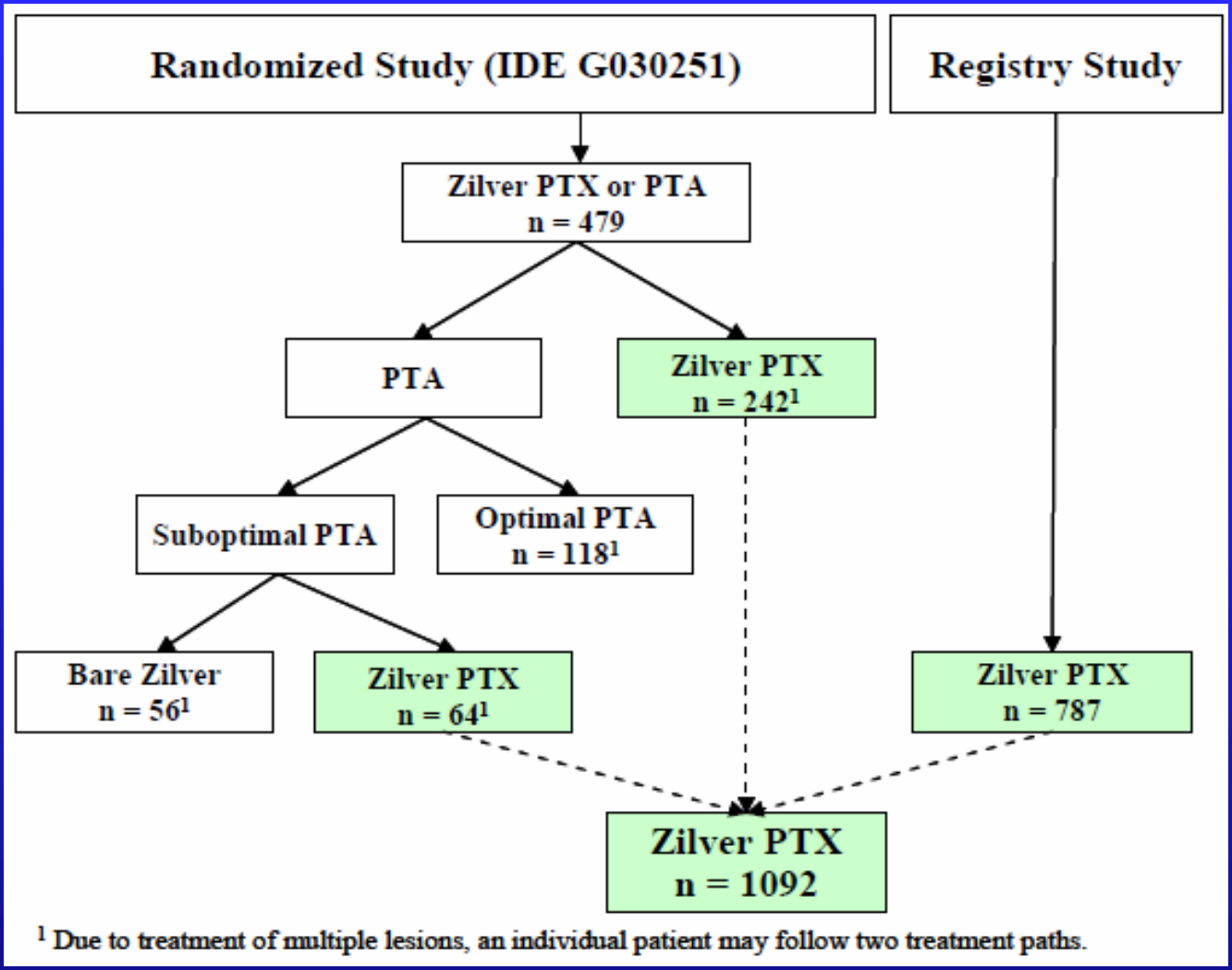


Months Post-Procedure	Estimate	Standard Error	Number Failed	Number Censored	Number Remaining
0	99.9%	0.1%	1	0	840
1	99.0%	0.3%	8	2	831
6	96.4%	0.6%	30	18	793
12	83.0%	1.3%	138	50	653

Summary of Clinical Evidence

RCT and Registry Studies

Summary



* AT Population

Safety and Effectiveness Endpoints

	RCT – PTA Control	RCT – Zilver PTX	Registry – Zilver PTX
Safety: 12 mo EFS	83.9%	90.4%	89.0%
Effectiveness: 12 mo Patency	32.7%	82.7%	83.1%

* KM Estimates

Stratification by Lesion Lengths

Lesion Length	Event Free Survival (# Subjects)		
	Optimal PTA	Bare Zilver	Zilver PTX
< 7 cm	80.4% (88)	85.8% (36)	92.7% (543)
7-14 cm	75.3% (26)	86.7% (15)	91.5% (296)
> 14 cm	50.0% (4)	100.0% (2)	79.6% (233)

Lesion Length	Primary Patency (# of Lesions)		
	Optimal PTA	Bare Zilver	Zilver PTX
< 7 cm	70.1% (93)	71.0% (40)	88.7% (616)
7-14 cm	45.0% (27)	70.6% (17)	83.6% (312)
> 14 cm	50.0% (4)	100% (2)	68.7% (222)

Zilver PTX Stent Integrity

Study	#Stents visualized by x-ray at 12 months	#Stents without fracture	#Stents with fracture	12 month Stent Integrity Rate	12-month Stent Fracture Rate
Randomized Study	457	453	4	99.1%	0.9%
Registry Study	1432	1410	22	98.5%	1.5%
Combined	1889	1863	26	98.6%	1.4%

Particulate Effects

	Peri-Procedure		> 30 Days	
Study	Bare Zilver	Zilver PTX	Bare Zilver	Zilver PTX
Randomized Study	1.8% (1/56)	0.3% (1/305)	0.0% (0/56)	1.3% (4/305)
Registry Study	-	0.8% (6/787)	-	0.0% (0/787)
Combined	1.8% (1/56)	0.6% (7/1092)	0.0% (0/56)	0.4% (4/1092)

Neutropenia

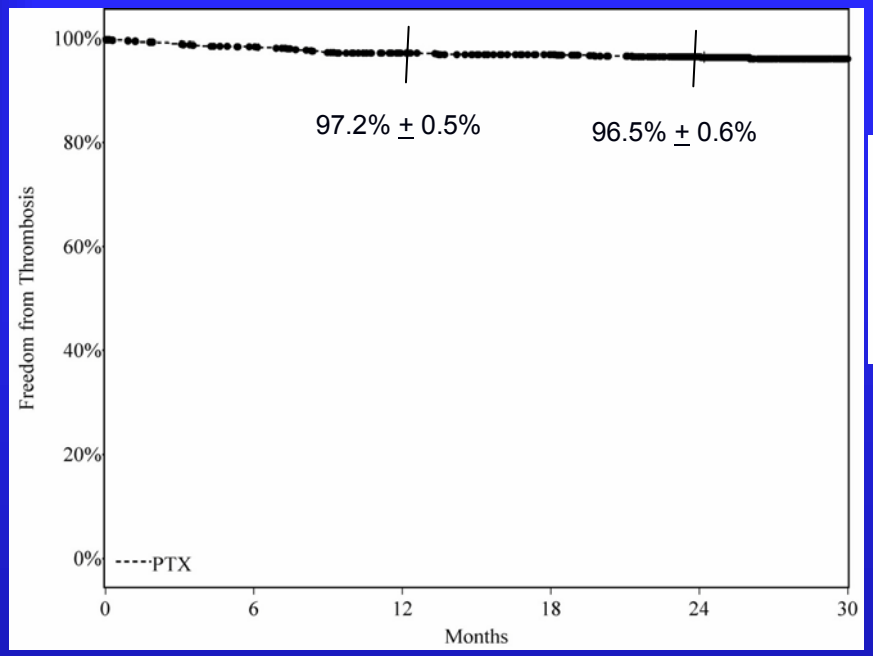
Absolute Neutrophil Count <1.5 x 1000/mm^3		
Study	**Bare Zilver**	**Zilver PTX**
Randomized Study	3.6% (2/56)	1.0% (3/305)
Registry Study	-	0.1% (1/787)
Combined	3.6% (2/56)	0.3% (4/1092)

Drug Hypersensitivity

- 33 total cases – 28 RCT, 5 Registry
- 0 attributed to paclitaxel or stent material
- 23/33 attributed to ASA, Clopidogrel, Ticlopidine
- 2 attributed to contrast material

Stent Thrombosis

All Zilver PTX Freedom From Stent Thrombosis
(KM Analysis)



Months Post-procedure	Freedom from Thrombosis Estimate	Standard Error	Cumulative Failed	Cumulative Censored	Number Remaining
0	99.9%	0.1%	1	0	1091
1	99.5%	0.2%	5	5	1082
6	98.4%	0.4%	17	19	1056
12	97.2%	0.5%	30	62	1000
24	96.5%	0.6%	37	292	763

Group	0 - 12 Months			0 - 24 Months		
	KM Estimate	Thromboses	Remaining	KM Estimate	Thromboses	Remaining
Provisional bare Zilver group	96.4%	2	51	96.4%	2	50
Zilver PTX treatment group	97.5%	6	219	97.1%	7	198
Zilver PTX treatment + Provisional Zilver PTX	98.0%	0	279	97.7%	7	256
All Zilver PTX (RCT & Registry)	97.2%	30	1000	96.5%	37	763

Review Team Conclusions

Clinical Conclusions

- RCT met pre-specified primary endpoints
- Sub-analyses support Safety & Effectiveness
  - Provisional PTX vs. Provisional Bare Zilver
  - Zilver PTX vs. Standard Therapy (optimal PTA + Bailout BMS)
- Global Registry - data on low frequency safety events

Clinical Conclusions

- Lesion Length
- Anti-Platelet Regimen – Considerations for labelling
- Bailout Stenting
- Stent Fracture
- Long term Follow-Up

FDA Presentations

- Allison Kumar
  Introduction
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- Allison Kumar
  Conclusions

Statistical Summary

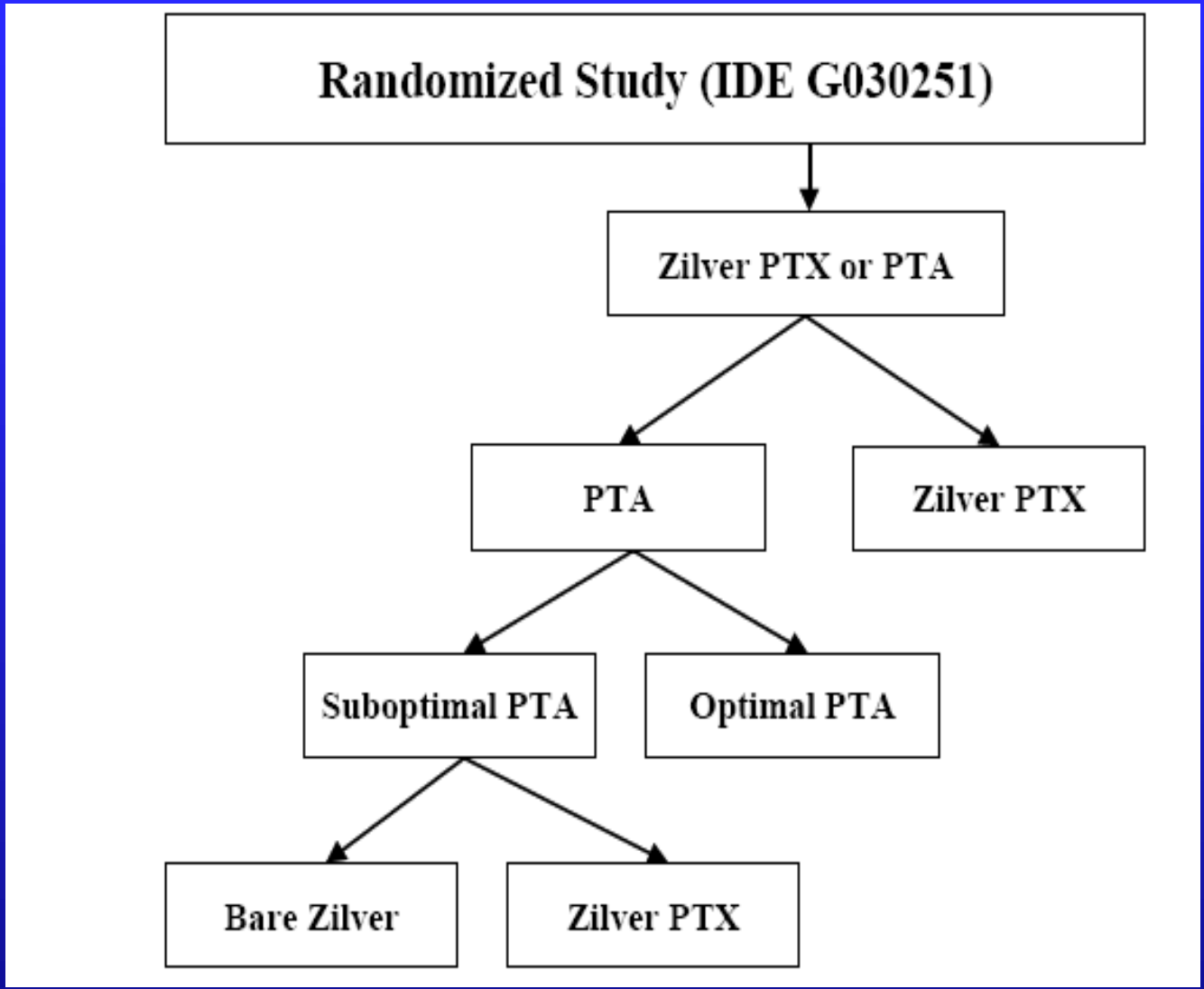
Xiting “Cindy” Yang, Ph.D.
Mathematical Statistician

Division of Biostatistics
Office of Surveillance and Biometrics

Outline

- Study analysis plan
- Study primary endpoint results
  - Primary safety endpoint
  - Primary effectiveness endpoint
  - Gender Analysis
- Summary

Pivotal Study Design



Patient Population

- Intent-to-treat (ITT)
  - All patients randomized to receive PTA / Zilver PTX at first randomization
- Per protocol (PP)
  - All patients randomized to receive PTA / Zilver PTX at first randomization; excluding those patients who did not receive initial PTA treatment
  - All patients randomized to receive Zilver PTX stent at first randomization; excluding those patients who did not receive a Zilver PTX stent
- As Treated (AT)
  - All patients who received PTA / Zilver PTX stent at first treatment

Primary Safety Endpoint

- Event-free survival (EFS) evaluated at 12-month
  - Defined as freedom from the Clinical Events Committee (CEC)-adjudicated major adverse events of death, target lesion revascularization, target limb ischemia requiring surgical intervention (bypass or amputation of toe, foot, or leg) or surgical repair of the target vessel (e.g., dissection or perforation requiring surgery), and freedom from worsening of the Rutherford classification by 2 classes or to class 5 or 6.
  - Events, including death, when not adjudicated to be device or procedure related, are not counted as events in the analysis.

Primary Safety Endpoint

- Hypotheses

  H_0: $EFS_{PTX} \leq EFS_{PTA} - \delta$

  H_A: $EFS_{PTX} > EFS_{PTA} - \delta$

  δ is 10%

- Analysis
  - Per-patient basis, PP population

$$Z = \frac{\hat{E}_{PTX} - \hat{E}_{PTA} + \delta}{SE}$$

  - $\hat{E}_{PTX}$ and $\hat{E}_{PTA}$ are Kaplan-Meier estimated EFS rates
  - SE: $\sqrt{\hat{V}(E_{PTX}) + \hat{V}(E_{PTA})}$
  - One-sided type I error rate of 0.05

Primary Effectiveness Endpoint

- Primary patency (PP) evaluated at 12-month
  - Assessed by duplex ultrasound or by angiography in cases when the duplex ultrasound is not interpretable.
  - Patency is defined as an open treated segment (i.e., < 50% diameter stenosis, including the region within ± 5 mm proximal and/or distal to the target lesion).

Primary Effectiveness Endpoint

- Hypothesis

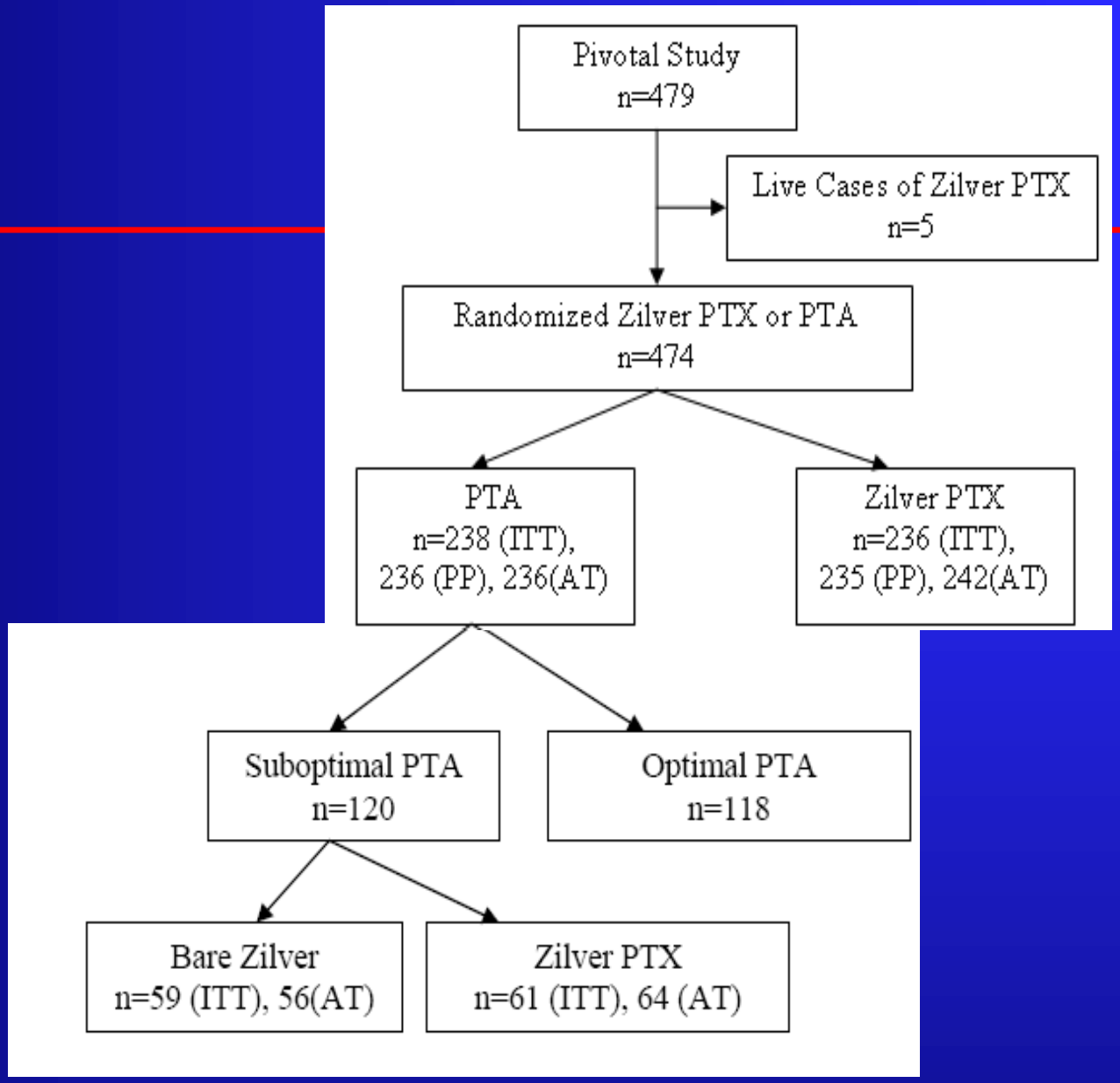
$$H_0: PP_{PTA} = PP_{PTX}$$
$$H_A: PP_{PTA} \neq PP_{PTX}$$

- Analysis
  - Per-lesion basis, ITT population
  - Z-statistics from GEE model
    - GEE model to account for possible correlation between lesions
  - Two-sided type I error rate of 0.05
  - Requires the observed primary patency rate of treatment be greater than that of control to claim success

Generalized Estimating Equation

- $E(Y_{ij})=\mu_{ij}$
- $g(\mu_{ij}) = X_{ij}\beta$
  - Y_{ij}: patency for patient i, lesion j
  - X_{ij} : covariate vector
  - β: coefficient vector
- Y_{ij} with the same i not necessarily independent
  - In this study, two lesions from the same patient might be correlated

Patient Accountability



Primary Safety Endpoint Results

- Non-inferiority test is met on PP population (235 pt. in Treatment and 236 pt. in Control)
  - Kaplan-Meier estimates
    - $\hat{E}_{PTX} = 90.4\%$
    - $\hat{E}_{PTA} = 83.9\%$
    - Difference($\hat{E}_{PTX} - \hat{E}_{PTA}$): 6.5% with 2-sided 95%C.I. (0.5%, 12.5%)
  - Non-inferiority test
    - P-value < 0.01
- Primary safety endpoint is also met on ITT and AT populations

Primary Effectiveness Endpoint Results

- Primary effectiveness endpoint is met on ITT population (247 lesions in treatment and 251 lesions in control)
  - GEE model estimates
    - PP_{PTX} = 75.9%
    - PP_{PTA} = 28.2%
  - Superiority test
    - P-value < 0.01
    - Treatment patency rate is higher
- Primary effectiveness endpoint is also met on PP and AT populations

Missing Data and Worst Case Analysis

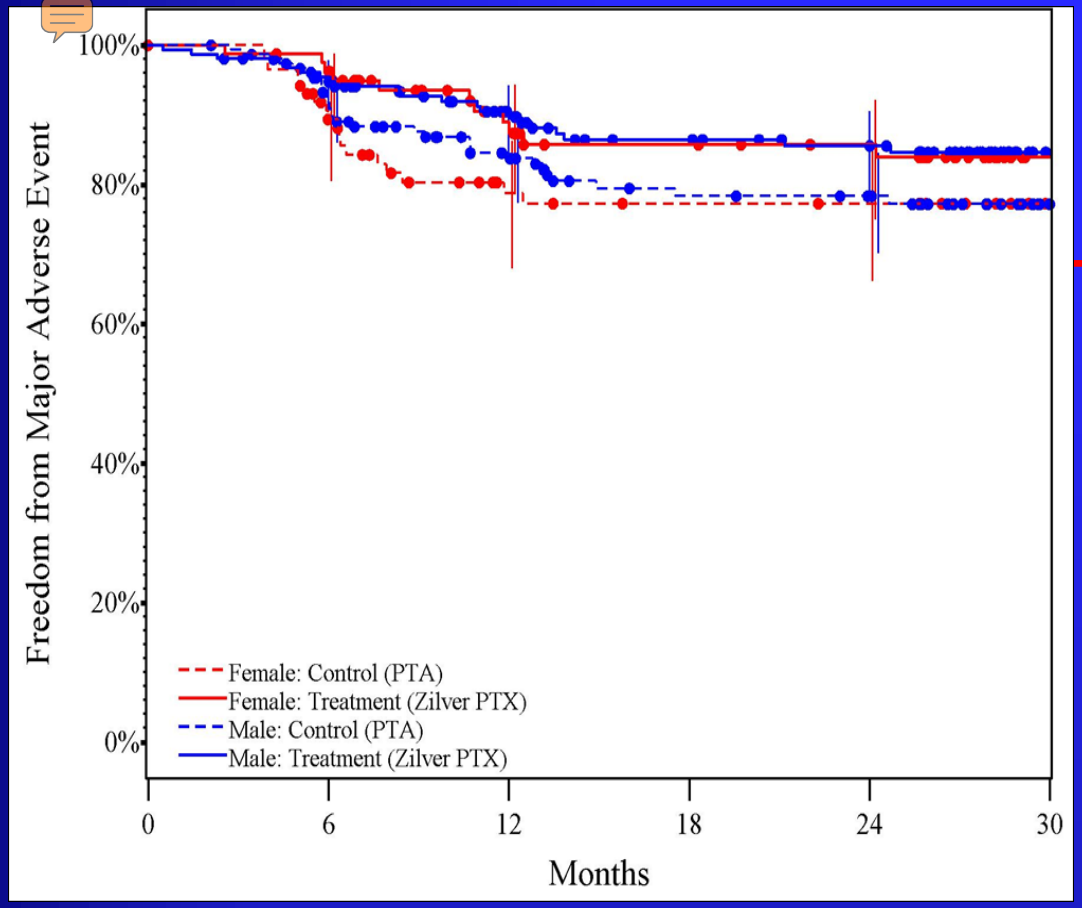
- About 8% missing data on the primary effectiveness endpoint (per-lesion)

Variable	Lesions with Missing Data					
	Intent-to-treat (ITT)		Pre-protocol (PP)		As-treated (AT)	
	PTA	PTX	PTA	PTX	PTA	PTX
Primary effectiveness endpoint	7.6% (19/251)	7.7% (19/247)	7.6% (19/249)	7.7% (19/246)	7.6% (19/249)	7.5% (19/253)

- Worst Case analysis
  - All missing in treatment are counted as failures
  - All missing in control are counted as successes
  - Still met primary effectiveness endpoint on all three populations

Group	Primary Patency (95% CI)		
	Intention-to-treat (ITT)	Per-protocol (PP)	As-treated (AT)
PTA control group	31.5% (25.9%, 37.6%)	31.0% (25.4%, 37.1%)	30.5% (25.0%, 36.7%)
Zilver PTX treatment group	70.1% (64.0%, 75.5%)	70.4% (64.3%, 75.8%)	71.3% (65.2%, 76.6%)

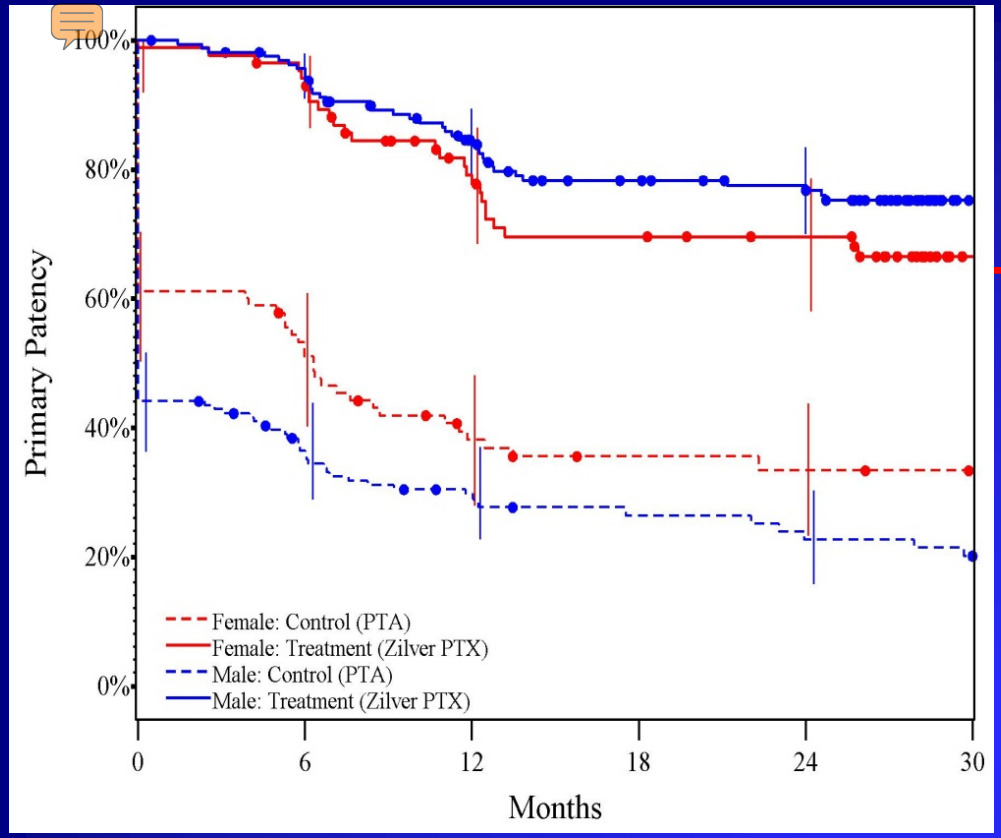
Gender Analysis (Safety)



- KM estimate
  - Female:
    - 88.9% for the treatment
    - 78.8% for the control
  - Male:
    - 90.5% for the treatment
    - 84.5% for the control

- Covariate Analysis (FDA initiated)
  - Logistic regression
  - Covariates: treatment, age, gender, body mass index, smoking status, diabetes, hypercholesterolemia, hypertension, carotid disease, renal disease, pulmonary disease, congestive heart failure, previous MIs, and previous diagnosis of cardiac arrhythmia , and treatment*gender interaction
  - No treatment*gender interaction detected

Gender Analysis (Effectiveness)



- KM estimate
  - Female:
    - 79.1% for the treatment
    - 38.1% for the control
  - Male:
    - 84.5% for the treatment
    - 29.7% for the control

- Covariate Analysis (FDA initiated)
  - GEE model
  - Covariates: treatment, gender, BMI, hypercholesterolemia, smoking status, total occlusion, lesion length, and treatment*gender interaction
  - P-value for treatment*gender interaction: 0.052

Summary of Randomized Study

- The primary safety endpoint appears to meet its pre-specified non-inferiority criterion.
- The primary effectiveness endpoint appears to meet its pre-specified superiority criterion.

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Post-Approval Study (PAS) Considerations

George K. Aggrey, MD MPH
Division of Epidemiology
Office of Surveillance and Biometrics

General Principles for Post-Approval Studies

- Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness
- Post-approval studies should <u>not</u> be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness

Need for Post-Approval Studies

- Gather postmarket information
  - Long-term performance including effects of re-treatments & device changes
  - Real-world device performance (patients and clinicians)
  - Effectiveness of training programs
  - Sub-group performance
  - Outcomes of concern (safety and effectiveness)
- Account for Panel recommendations

Post-Approval Study Components

- Fundamental study question or hypothesis
- Safety endpoints and methods of assessment
- Acute and chronic effectiveness endpoints and methods of assessment
- Duration of follow-up

Zilver PTX Postmarket Issues

- Long-term (5-year) major adverse events in the post-approval study population
- 5-year risk of stent thrombosis and stent fracture
  - Premarket (randomized + registry) 1-year incidence:
    - 1.4% Fracture
    - 2.8% Thrombosis (KM estimate)

Outline of Sponsor's Proposed PAS

Hypothesis	H0: $EFS_{PTX} - EFS_{PTA} \geq \delta$ H1 : $EFS_{PTX} - EFS_{PTA} < \delta$ Where: ■ EFS_{PTX} and EFS_{PTA} is event-free survival in Zilver PTX and PTA groups, respectively ■ δ is non-inferiority margin = 10%
Study Design	Continued follow-up through 5 years of IDE RCT study patients. Evaluation at yearly intervals.
Sample Size	Up to 217 Zilver PTX patients and 222 PTA control patients from the IDE RCT. ■ 113 patients per group with 5 years f/u data

Outline of Sponsor's Proposed PAS – Sample Size Calculations

- 113 per treatment group
  - Kaplan-Meier estimates of EFS at 60 months
    - Zilver PTX stent treatment group = 77.8%
    - PTA control group = 73.6%
  - exact non-inferiority test for two binomial populations
  - delta = 0.10
  - alpha = 0.05
  - power = 0.80
  - loss to follow-up rate = 5% per year

Outline for Proposed PAS

Primary Safety Endpoints	•**<u>5-year composite:</u>** -Death -TLR -Target limb ischemia, surgical repair of target vessel -Worsening Rutherford Classification by 2 classes or to Class 5/6
Statistical Analysis	•Kaplan Meier estimates of event free survival compared using Z-statistics •The primary safety H_0 will be rejected if $\hat{EFS}_{PTX} - \hat{EFS}_{PTA} > Z_{\alpha} SE - \delta$, for $\alpha = 0.05$
Secondary Safety Endpoints	•Stent fracture at 5 years (flat-plate x-ray) •Late Stent thrombosis at 5 years

FDA Assessment – PAS Outline

- Endpoints assess long-term safety and stent integrity at 5-years
  - Primary and secondary endpoints and length of follow-up are appropriate
- Premarket registry subjects only consented out to 2 years
  - Possible selection bias introduced through re-consenting
- Proposed inclusion of PAS broad range of institutions globally
  - Generalizability to the US population may be limited
- The sample size proposed by the sponsor (n =900) does not account for losses to follow-up

FDA Sample Size Rationale

- In the premarket study, the sponsor calculated that in order to establish the rates of late rare events, 900 patients would be sufficient.

- Rare events: Stent thrombosis, stent fracture (1-2%)
  - Assumed rate = 1%
    - 1-sided 95% upper bound = 1.74%
    - sample size = 898
  - Assumed rate = 2%
    - 1-sided 95% upper bound = 2.95%
    - sample size = 903
- Based on the premarket follow-up it's reasonable to expect 11% loss to follow-up at 5 years.

Panel Questions

- Please comment on the need to enroll additional subjects as part of a post-approval study.
- Please comment on whether subjects from the global registry could be re-consented for longer-term follow-up without introducing selection bias.
- Please also comment on the appropriateness of leveraging data collected from new subjects enrolled from outside the US.
- Please comment on any other aspects of the post-approval study.

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Conclusions

- The Zilver PTX Study met the pre-specified safety and effectiveness endpoints
- The Zilver PTX Study did not raise any safety concerns
- Significance of late term rare events unknown
- Sub-analyses comparing various treatment strategies suggested a benefit for the Zilver PTX stent
- Long-Term Follow-up Availability and Results
- Post-market follow-up

Thank you