AMPLATZER Patent Foramen Ovale (PFO) Occluder

FDA Review of P120021

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Office of Device Evaluation
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration

May 24, 2016

FDA Presentations

- **Introduction and Regulatory History**
  - **Dr. Arielle Drummond**
- Statistical Presentation
  - Dr. Rong Tang
- Clinical Presentation
  - Dr. Andrew Farb
- Post-Approval Considerations
  - Dr. Erika Tang
- Summary
  - Dr. Arielle Drummond

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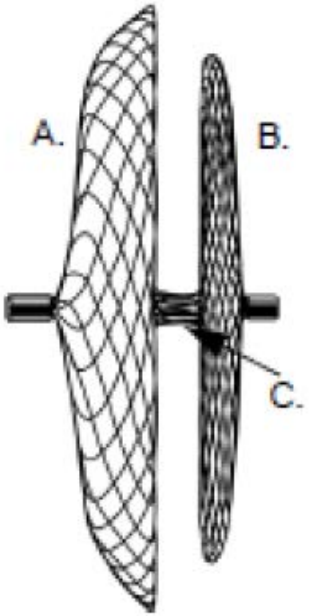
Device Description

- AMPLATZER PFO Occluder System includes:
  - AMPLATZER PFO Occluder (shown right, 3 sizes available)
  - TorqVue Delivery System



A. Right atrial disc
B. Left atrial disc
C. Waist

Non-Clinical Testing

- Bench Studies
- Biocompatibility
- MRI Compatibility
- Animal Studies
- Sterilization
- Shelf-Life/Packaging
- Manufacturing (QS/GMP)

Non-clinical testing was found acceptable

Proposed Indications for Use

Indications for Use:

The AMPLATZER PFO Occluder is intended for percutaneous, transcatheter closure of a patent foramen ovale (PFO) to prevent recurrent ischemic stroke in patients who have had a cryptogenic stroke due to a presumed paradoxical embolism.

Regulatory History

- IDE Approved – September 2000
  - First subject enrolled in pivotal study September 2003
  - Multiple clinical protocol revisions primarily intended to address slow enrollment and to include supplementary statistical analyses
  - Enrollment closed December 2011
- PMA Submitted – November 2012
  - Initial PMA data lock – 20 May 2012
  - Extended Follow-up – 14 August 2015

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FDA Statistical Review
AMPLATZER PFO Occluder

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Center for Devices and Radiological Health
CDRH

Outline

- RESPECT Study Design
- Analysis Populations
- Trial Results
- Statistical Summary

RESPECT Study Design

- The RESPECT Trial is a prospective, multicenter, randomized (1:1), event-driven, open label, superiority clinical trial

Study Timeline

- Enrollment period: 8 years (2003 to 2011)
  - Initial data lock on 20 May 2012 (original PMA analysis), a total of 25 events and 2760 patient years observed
  - Data lock date on 14 Aug 2015 (extended follow up analysis), a total of 42 events and 5154 patient years observed

Primary Analysis Group

- Two study arms
  - Test: AMPLATZER PFO Occluder (Device) + Medication
  - Control: Medical management (MM)
- 1:1 Randomization (980 subjects)
  - 499 randomized to the test (Device + medication) group
  - 481 randomized to the control (MM) group

Primary Effectiveness Endpoint Composite

- A composite of
  - Recurrence of a nonfatal stroke
  - Fatal ischemic stroke
  - Post-randomization death
    - Test group: all-cause mortality within 30 days after implant or 45 days after randomization, whichever occurs last;
    - Control group: 45 days after randomization

Pre-Specified Statistical Analyses

- Raw count analysis (superiority)

$$H0: r_1 \geq r_2 \qquad \text{vs} \qquad H1: r_1 < r_2$$

Fisher's Exact test at alpha level is two-sided 0.05

– where r_1 and r_2 are the rate of recurrent nonfatal stroke, post-randomization death or fatal ischemic stroke for the device and MM groups respectively

– Pre-specified analysis population: Intention-to-treat (ITT) population

Study Decision Rule for Device Superiority (Effectiveness Endpoint)

- **Stage 1**: Enrollment would be stopped and Device **superiority** would be declared if within the first 12 events, the number of primary endpoint events for the MM group equals or exceeds 10.
- **Stage 2**: Enrollment would be stopped once 25 events were observed. Device **superiority** would be declared if within the first 25 events, the number of primary endpoint events for the MM group equals or exceeds 19.

Supplementary Statistical Analyses

- Survival analysis (log-rank test) was later added
- Analysis populations added in addition to the ITT population
  - Per-Protocol (PP) , As Treated (AT), and Post-Hoc Device in Place (DIP) populations

Study Population

- In accordance with the pre-specified decision rule, trial enrollment was stopped once 25 primary endpoint events occurred.
- 980 subjects enrolled
  - 499 randomized to the AMPLATZER PFO Occluder (treatment) group
  - 481 randomized to the Medical Management (control) group

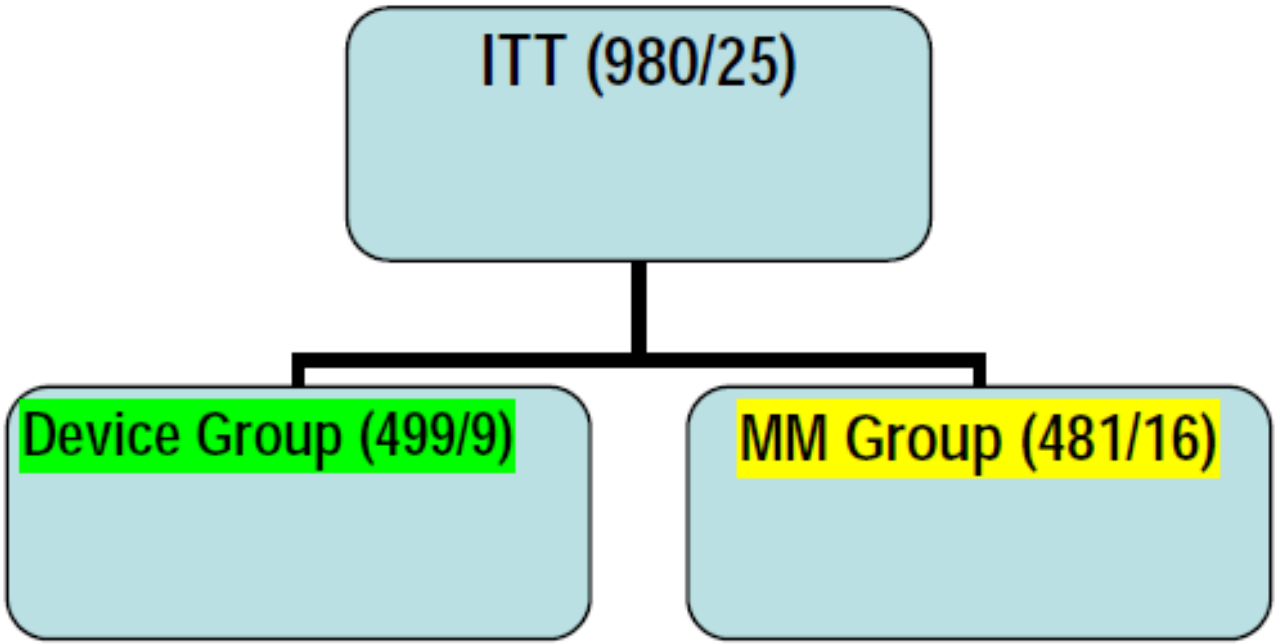
Analysis Populations

- Proposed prior to enrollment stopping
  - Intent to treat
  - Per-Protocol
  - As Treated
- Proposed after enrollment stopped
  - Post-Hoc Device in Place

ITT Population

- Intention-to-treat (ITT), where all randomized subjects are analyzed within the group to which they were randomized.
- FDA draft guidance recommends that the primary statistical analysis follow the ITT principle for randomized clinical superiority trials.
  - avoid biases associated with patients switching treatment, selection bias, and dropout/withdrawal patterns that may confound the observed treatment effect.

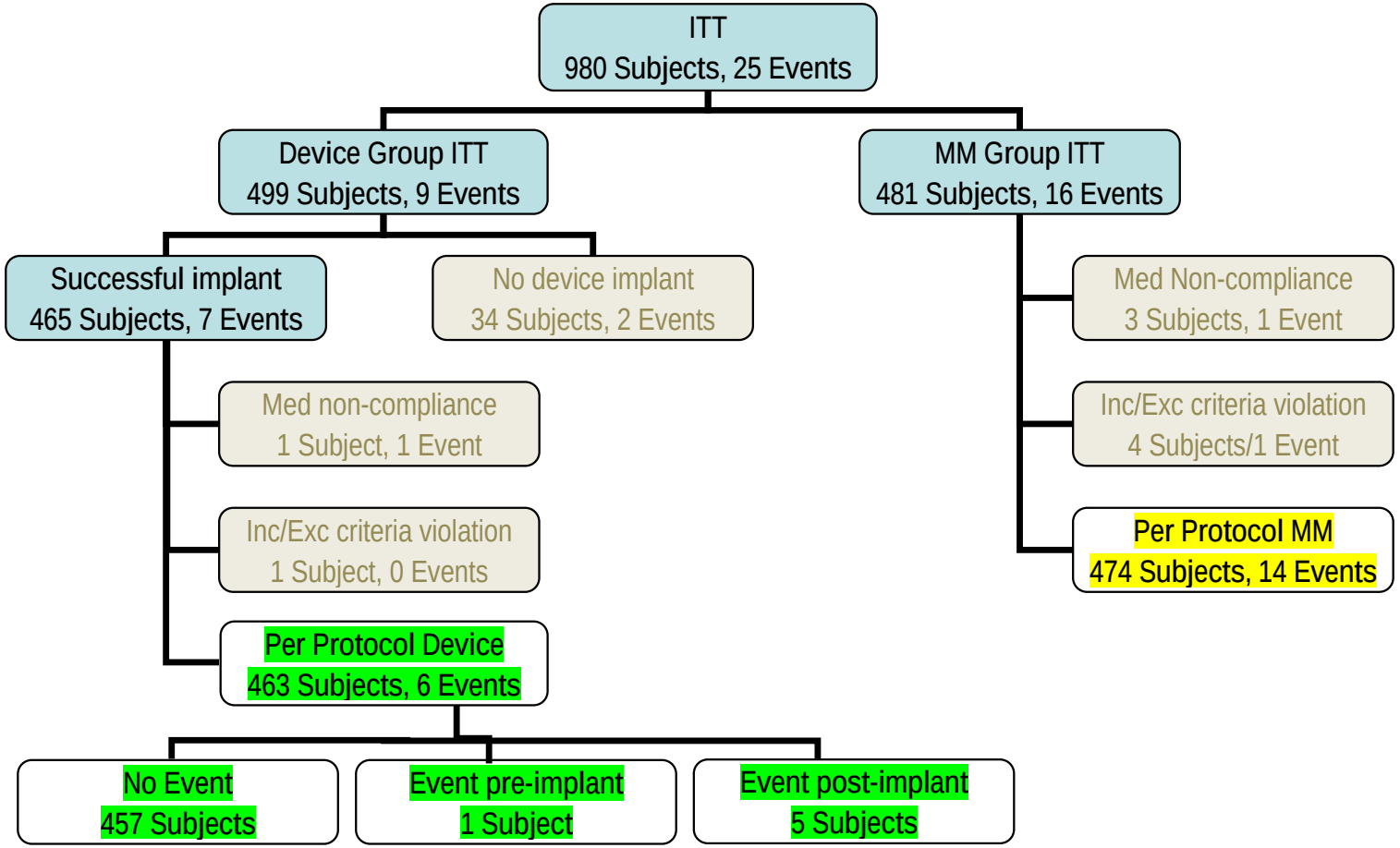
Subject Accountability – ITT



Per Protocol (PP) Population

- Test group (463)
  - 463 Device group subjects who received a device, met key eligibility criteria and were >67% compliant with prescribed medical regimen
- Control group (474)
  - 474 MM group subjects who met key eligibility criteria and were >67% compliant with prescribed medical regimen

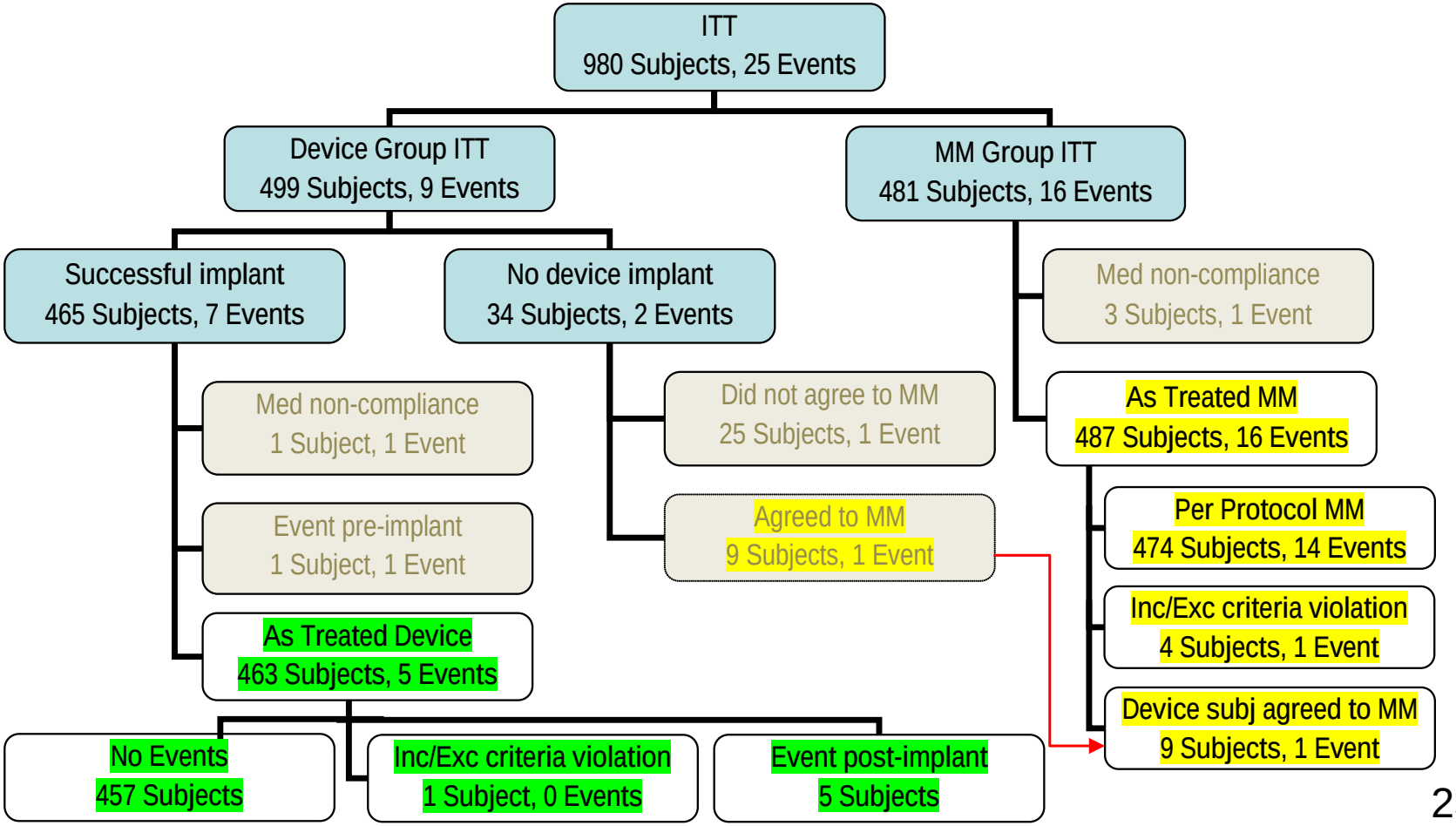
Subject Accountability – Per Protocol Population



As Treated (AT) Population

- Test group (463)
  - 463 device group subjects who received a device and were >67% compliant with prescribed medical regimen
- Control group (487)
  - 478 MM group subjects who were >67% compliant with prescribed medical regimen and
  - 9 device group subjects who refused the device but agreed to be followed in a protocol-approved medication regimen and were >67% compliant with prescribed medical regimen

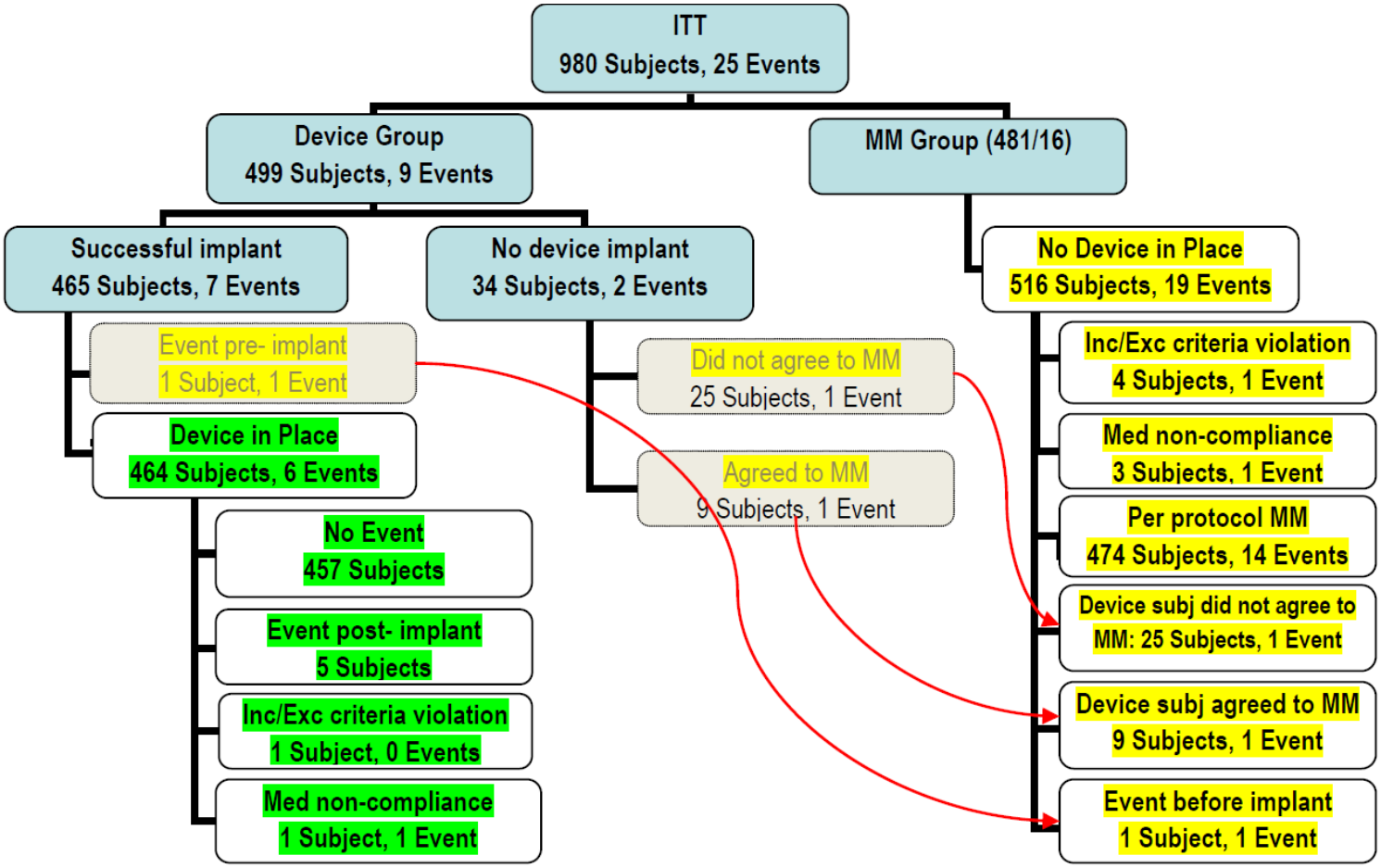
Subject Accountability-As Treated Population



Post hoc Device in Place (DIP) Population

- Test group (464 device in place)
  - Device subjects who were implanted with a device prior to the time of the primary endpoint event
- Control group (516 no device in place arm)
  - 1 device subject who had an event prior to implantation
  - 34 device subjects who refused device
  - 481 MM subjects

Subject Accountability-Device in Place Population



Study Results

- Pre-specified decision rule/raw count analysis
- Supplementary survival analysis results
  - ITT population
  - PP analysis results
  - AT analysis results
  - DIP analysis results

Raw Count Analysis Result

- Odds ratio 0.534 (0.234, 1.220) with P value 0.157 (ITT, initial lock)
  - Superiority cannot be claimed
  - Interpretation unclear
- Event per 100 patient years

	Device	**MM**
ITT/Initial lock	0.61 (9/1476)	1.2 (16/1284)
ITT/Extended lock	0.65 (18/2769)	1.0 (24/2376)

Conclusion per Decision Rule

- Pre-specified decision rule: the number of events for the control group should be ≥19 (out of 25) to claim treatment superiority
- RESPECT trial result:
  - 9 events in test group
  - 16 events in control group **(less than the 19 needed for superiority claim)**
- Conclusion: did not meet the decision rule, superiority cannot be claimed

Primary Endpoint Supplementary Analyses Results (D vs MM)

Initial Data Lock

Cohort Analysis	Subjects N total (N_D/N_{MM})	Primary Endpoint Events N total (N_D/N_{MM})	Hazard ratio (95% CI)	Nominal P value*
ITT/KM (initial)	980 (499/481)	25 (9/16)	0.500 (0.221, 1.131)	0.089*
PP/KM(initial)	937 (463/474)	20 (6/14)	0.371 (0.14, 0.97)	
AT/KM (initial)	950 (463/487)	21 (5/16)	0.280 (0.101, 0.755)	
DIP/KM (initial)	980 (464/516)	25 (6/19)	0.304 (0.122, 0.763)	

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Extended Follow-up Data Lock

Cohort Analysis	Subjects N total (N_D/N_{MM})	Primary Endpoint Events N total (N_D/N_{MM})	Hazard ratio (95% CI)	Nominal P value*
ITT/KM (extended)	980 (499/481)	42 (18/24)	0.65 (0.35, 1.20)	0.16*
PP/KM(extended)	937 (463/474)	37 (15/22)	0.58 (0.30, 1.12)	
AT/KM (extended)	950 (463/487)	38 (14/24)	0.51 (0.26, 0.99)	
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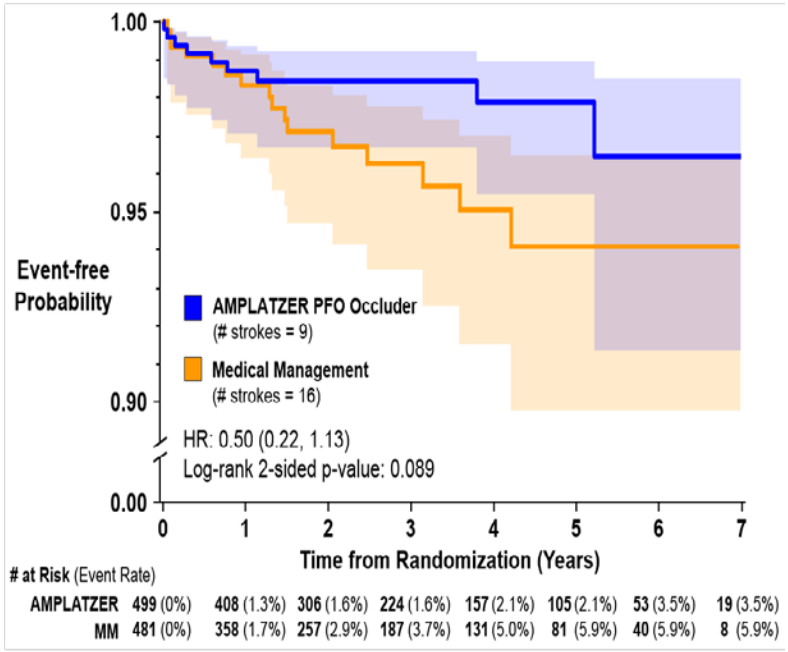
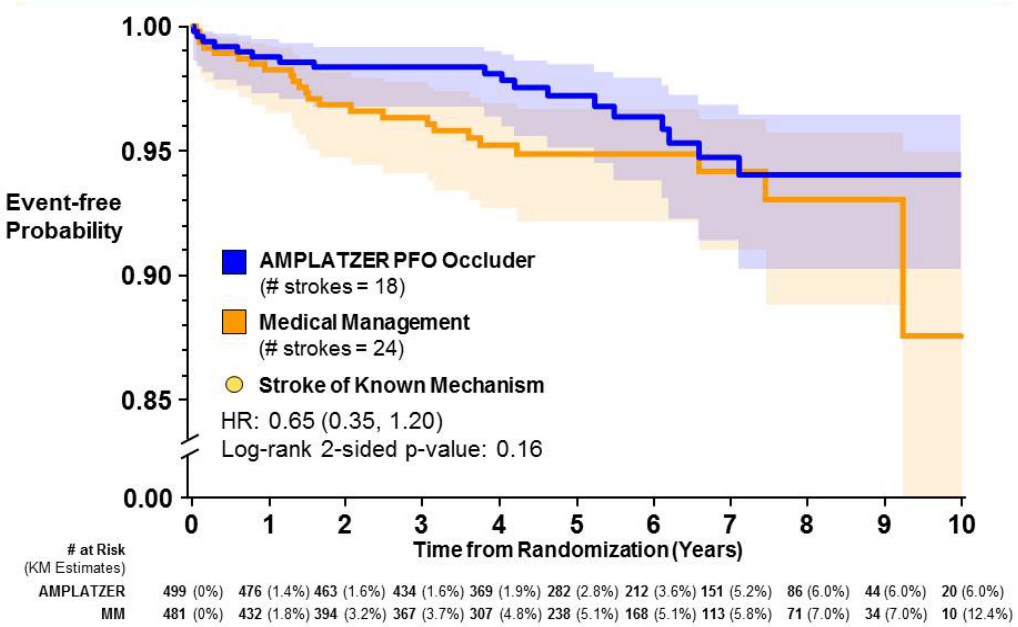
Freedom from Primary Endpoint Event
ITT analysis

Initial Data Lock

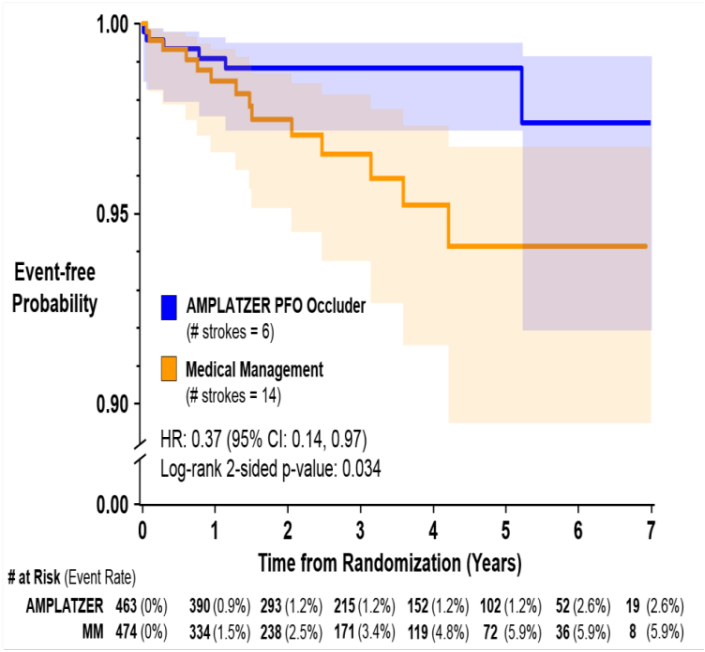


Extended Follow-up

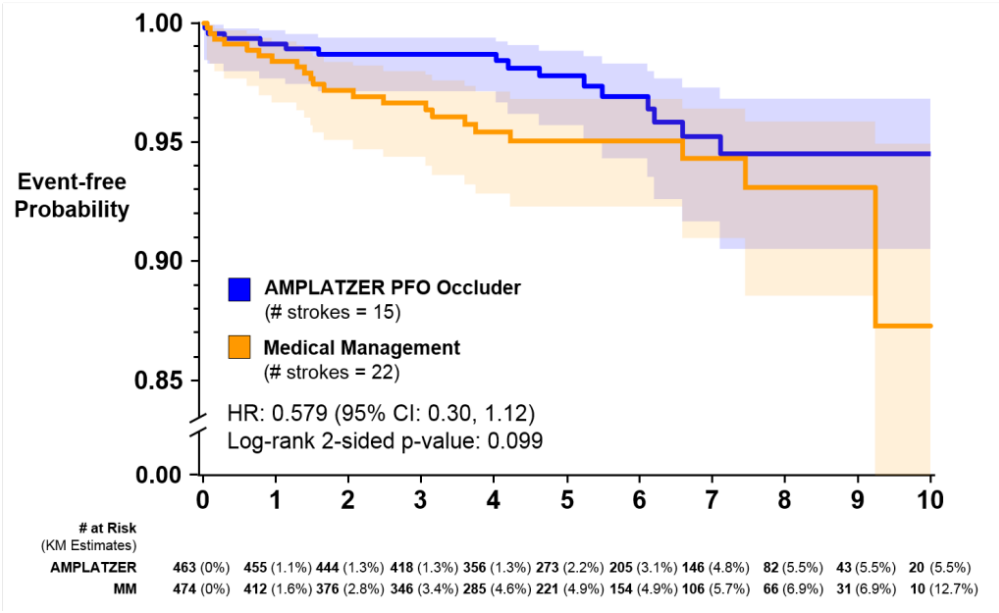


Freedom from Primary Endpoint Event Per Protocol Analysis

Initial Data Lock



Extended Follow-up



Subject Discontinuation

	Initial PMA Data Lock 20 May 2012		Extended Follow-up Data Lock 14 Aug 2015	
Disposition	Device (N=499)	MM (N=481)	Device (N=499)	MM (N=481)
Ongoing	447/499 (89.6%)	389/481 (80.9%)	408/499 (81.8%)	336/481 (69.9%)
Discontinued	52/499 (10.4%)	92/481 (19.1%)	91/499 (18.2%)	145/481 (30.1%)
Patient Death	3/499 (0.6%)	6/481 (1.2%)	6/499 (1.2%)	10/481 (2.1%)
Subject withdrawn	24/499 (4.8%)	55/481 (11.4%)	31/499 (6.2%)	71/481 (14.8%)
Lost to Follow-up	22/499 (4.4%)	28/481 (5.8%)	50/499 (10.0%)	59/481 (12.3%)
Investigator request	3/499 (0.6%)	3/481 (0.6%)	3/499 (0.6%)	4/481 (0.8%)
Other	0/0 (0.0%)	0/0 (0.0%)	1/499 (0.2%)	1/481 (0.2%)

Comment on Sensitivity analysis

- The primary analysis in the ITT population is not statistically significant.
- The sponsor performed tipping point analyses for per-protocol population using logrank test. That analysis shows device success in over 75% of the situations studied.
- Per-protocol is a post-randomization subgroup.
- Large number of missing value and small number of events

Selected Boundary Points from Tipping Point Analysis

PP	Device (34 missing)	MM (83 missing)	P value
Progressively change the censoring time to a primary endpoint event time in the MM group subjects who were discontinued prior to experiencing a primary endpoint, starting from the latest to the earliest. For the device group, starting from the earliest to the latest.	6+1	14	0.0642
	6+2	14	0.1098
	6+2	14+1	0.07
Progressively change the censoring time to a primary endpoint event time in the Device group subjects who were discontinued prior to experiencing a primary endpoint, starting from the latest to the earliest. For the MM group, starting from the earliest to the latest.	6+1	14	0.0587
	6+2	14	0.0941
	6+2	14+1	0.0652

Statistical Summary

- The superiority objective of the primary endpoint was not met.
- The extended follow-up analyses did not strengthen the treatment effect observed in the initial data lock.
- The PP, AT, DIP populations are post-randomization subgroups and these supplementary analyses results should be interpreted with caution.
- Differential discontinuation rates across study arms challenge the non-informative censoring assumption required for survival analysis.

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FDA Clinical Review
AMPLATZER PFO Occluder

Andrew Farb, MD
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration

Outline

- Stroke and PFO
- The RESPECT Trial
  - Trial design
    - Enrollment criteria
    - Cryptogenic stroke determination
    - Concomitant medical therapy
  - Trial results
    - Effectiveness endpoints
    - Safety assessments
  - RESPECT and PC trial meta-analysis
- Clinical review summary

Stroke

- Fourth leading cause of mortality and a leading cause of serious, long-term disability in the US
- Categorized as ischemic (>80% of all strokes), hemorrhagic, or undetermined
- In patients under 55 years of age, up to 30% of ischemic strokes reported to be cryptogenic (no identified cause)

Etiologies for Non-Cryptogenic vs. Cryptogenic Ischemic Stroke

Non-cryptogenic stroke

- Thrombo- or atheroembolism
  - Atrial fibrillation/atrial flutter
  - Left ventricular mural thrombus
  - Valvular endocarditis
  - Prosthetic heart valves
  - Thoracic aortic or carotid atherosclerosis
  - Venous thrombosis with right to left shunt
- Intracranial arterial disease
  - Atherosclerosis
  - Arterial dissection
  - Vasculitis
  - In situ thrombosis with a hypercoagulable state

Cryptogenic Stroke

- Diagnosis of exclusion
- Determination that a stroke is cryptogenic highly dependent on the comprehensiveness of the evaluation to exclude alternative known stroke etiologies

PFO

- Common incidental finding, present in 25-30% of individuals
- PFO presence not associated with increased stroke risk among asymptomatic individuals
  - Northern Manhattan Study (NOMAS):[1] PFO not associated with increased stroke risk in men and women, or in those younger or older than 60 years
  - Olmsted County SPARC Study:[2] PFO not an independent predictor of stroke among normal individuals >45 years old

[1]Di Tullio MR, et al. J Am Coll Cardio 200;49:797– 802.
[2]Meissner I, et al. . J Am Coll Cardiol 2006;47:440–5.

PFO and Stroke: Observational Studies

- Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS)
  - PFO detected by TEE in 33.8% of subjects
  - PFO present in 39.2% of subjects with a cryptogenic stroke vs. 29.9% of subjects with a known etiology for stroke (Homma, 2002)
- PFO as a potential risk in young patients with stroke
  - PFO-ASA Study: PFO identified by TEE in 45.9% of young subjects with cryptogenic stroke (higher than the prevalence of PFO in the general population). (Lamy, 2002)
  - PFO prevalence 43.9% in patients age ≤55 years with cryptogenic stroke vs. 14.3% in patients with stroke due to a known cause (Handke, 2007)

PFO and *recurrent* stroke (i.e., a second stroke)

PICSS study: Stroke patients with PFO did not have a significantly increased risk of recurrent stroke or death at 2 years compared to stroke subjects without a PFO

PFO Morphology and Shunt and Confirmation of Paradoxical Embolism

- No consistent association established between the risk of stroke and:
  - PFO size
  - Severity of right-to-left interatrial shunt
  - Presence of an ASA
- Case reports of thrombi originating in the venous circulation traversing a PFO in stroke patients, but venous thrombosis only rarely identified in patients with PFO and stroke.

2014 Professional Society Therapy Guidelines

For patients with an ischemic stroke or TIA and a PFO who are not otherwise being treated with anticoagulation:

- Antiplatelet agents recommended (Class I; LOE B)
  - Insufficient data to establish whether anticoagulation is equivalent or superior to ASA for secondary stroke prevention in patients with a PFO (Class IIb; LOE B)

Regarding transcatheter device closure of a PFO, available data do not support a benefit to reduce the risk of recurrent stroke (Class III; LOE A).

Kernan WN, et al. 2014 AHA and ASA guidelines (affirmed by the American Academy of Neurology). *Stroke* , 45: 2160–2236

Studies to Collect Definitive Evidence of the Safety and Effectiveness of PFO Closure to Reduce the Risk of Recurrent Stroke

- FDA has advocated the need for randomized controlled trials
- FDA's position supported by:
  - Circulatory System Devices Advisory Panel on three occasions (October 24, 1997, September 10, 2002, and March 2, 2007)
  - Cardiovascular and Neurology professional societies

Randomized Trials of PFO Closure to Prevent Recurrent Stroke in PFO Patients

- CLOSURE I: Failed to show superiority of the STARFlex PFO Occluder vs. medical therapy for the composite primary endpoint of:
  - Recurrent stroke or TIA at 24 months
  - All-cause mortality to 30 days
  - Death from neurologic causes between 31 days and 24 months
- PC trial: PFO closure with the Amplatzer PFO Occluder not superior to medical therapy for the composite primary endpoint of:
  - Death
  - Nonfatal stroke
  - TIA
  - Peripheral embolism

The RESPECT Trial

Objectives and Design

- **Objective:** To investigate whether percutaneous PFO closure is superior to current standard of care medical treatment for the prevention of recurrent embolic stroke in subjects who had a cryptogenic stroke
- **Design:** Prospective, multicenter, randomized, unblinded study
  - Neither subjects nor health care providers were blinded to the randomization assignment

Randomization

- Randomized 1:1
  - Test group: Amplatzer PFO Occluder (the Device)
  - Control: Medical management (MM)
- Randomization stratification
  - Investigational site
  - Presence of an atrial septal aneurysm (ASA)
  - Recommended medical therapy

Key Inclusion Criteria

- PFO and a cryptogenic stroke within 270 days
  - Stroke defined as an acute focal neurological deficit, presumed to be due to focal ischemia, and either:
    1. Symptoms persisting ≥24 hours, or
    2. Symptoms persisting ≤24 hours with MR or CT findings of a new, neuroanatomically relevant, cerebral infarct
  - Cryptogenic stroke defined as a stroke of unknown cause
  - PFO defined as visualization of microbubbles (during TEE) in the LA within three cardiac cycles of RA opacification at rest and/or with Valsalva

General Exclusion Criteria

- Age <18 years and age >60 years
- MI or unstable angina within 6 months
- Mitral or aortic valve stenosis or severe regurgitation
- LVEF <35%
- Kidney, liver or lung failure
- Uncontrolled hypertension or diabetes mellitus despite medications
- Subjects contraindicated for aspirin or clopidogrel
- Subjects not able to discontinue anticoagulation if randomized to the Device
- Qualifying stroke with Modified Rankin score >3
- Anatomy in which the Device would interfere with intracardiac or vascular structures

Exclusion Criteria - Potential Embolic Etiologies Independent of PFO Presence

Cardiac

- Atrial fibrillation/atrial flutter (chronic or intermittent)
- LV aneurysm, intracardiac thrombus, or tumor
- Mitral or aortic valve vegetation or prosthesis
- Aortic arch plaques protruding >4 mm into the lumen

Non-cardiac

- Atherosclerosis or arteriopathy of intra- or extracranial vessels with >50% diameter stenosis
- Another cause of right-to-left shunting (e.g., an ASD or a fenestrated atrial septum)

Exclusion Criteria – Non-Embolic Qualifying Stroke

- Lacunar infarct in the distribution of a single, small deep penetrating vessel with any of the following:
  - HTN
  - Diabetes mellitus
  - Age ≥50 years, or
  - MRI or CT with European Task Force Age-Related White Matter Changes score >0
- Arterial dissection
- Hypercoagulable state, defined as any of the following:
  - Anticardiolipin antibodies
  - Lupus anticoagulant
  - B2-glycoprotein-1 antibodies, or
  - Elevated plasma homocysteine despite medical therapy

RESPECT Baseline Screening Tests for Cryptogenic Stroke Determination

- Work-up of qualifying stroke evaluated by a neurologist
- TEE
- ECG or Holter monitor
- Brain MRI or CT scan
- Imaging of intracranial arteries via MR angiography (MRA), CT angiography (CTA), contrast arterial angiography, or transcranial Doppler
- Imaging of extracranial arteries via MRA, CTA, contrast arterial angiography, or duplex ultrasound
- Hypercoagulability panel

Take Home Messages From RESPECT Enrollment Criteria

- Qualifying stroke confirmed by a neurologist
- PFO confirmed by TEE
- Comprehensive work-up to exclude known causes of ischemic stroke
  - Neurologic and neurovascular evaluation
  - Cardiovascular evaluation

Adjunctive Anti-Thrombotic Medical Therapy

Device Group
Protocol-Directed Medical Therapy

- **Pre-implant procedure:** Aspirin (325 mg/day) for at least 24 hours prior to the procedure.
- **Post-implant procedure:**
  - Clopidogrel and aspirin for 1 month
  - Aspirin alone through 6 months after Device implantation
  - After 6 months, medical therapy was at the physician's discretion

MM Group Protocol
Directed Medical Therapy

Any of the following regimens acceptable for MM subjects:

- Aspirin alone
- Warfarin alone
- Clopidogrel alone
- Aspirin plus dipyridamole
- Aspirin plus clopidogrel (later removed as an acceptable medical regimen per the 2006 update of the AHA/ASA guidelines)

Heterogeneity of Anti-Thrombotic Therapy

There is no recognized standard-of-care anti-thrombotic medical therapy to reduce the risk of recurrent stroke in patients with cryptogenic stroke.

- The use of multiple combinations of anti-thrombotic agents in the MM group presents challenges in defining the probable benefits of the Device vs. medical therapy.

MM Group Anti-Thrombotic Medical Therapy Caveats

- Investigators determined the recommended medication regimen for each subject.
- MM subjects were allowed to change medical treatment as long as the new regimen was included among the protocol-defined options.

Device Group Anti-Thrombotic Therapy Use in RESPECT

Approximately 90% of Device subjects were taking anti-thrombotic medications throughout the study

- Vast majority of Device subjects used antiplatelet agents

The RESPECT trial is essentially a study of the Device + MM vs. MM alone

MM Group Use of Protocol-Directed Medical Therapy

- Use of protocol-directed anti-thrombotic medical therapy (antiplatelet agents or warfarin, alone or in combination) was high throughout the trial.
  - Except for very late follow-up time points (in which data are limited), use of anti-thrombotic medications was >95% at all follow-up assessments.

Per-Protocol Anti-Thrombotic Medication Non-Compliance

- Medication non-compliance defined as <67% cumulative compliance over the course of the study.
- There is no evidence-based definition of anti-thrombotic therapy non-compliance in patients with cryptogenic stroke that establishes a threshold associated with recurrent events or risk reduction.

RESPECT Trial Endpoints

Primary Effectiveness Composite Endpoint

- Recurrent nonfatal stroke
- Fatal ischemic stroke
- Post-randomization all-cause mortality
  - **Device group:** Death within 30 days after implant or 45 days after randomization (whichever occurs latest)
  - **MM group:** Death within 45 days after randomization

Primary Effectiveness Composite Endpoint

- All events were recurrent nonfatal strokes
- Fatal ischemic stroke
- Post-randomization all-cause mortality
  - **Device group:** Death within 30 days after implant or 45 days after randomization (whichever occurs latest)
  - **MM group:** Death within 45 days after randomization

Major Secondary Effectiveness Endpoints

- TIA
- **Device group only:** Complete PFO closure at 6 months follow-up assessed by TEE bubble study
  - Absence of microbubbles in the left atrium at rest and during Valsalva within 3 cardiac cycles after right atrial opacification
  - Adjudicated by the Echo Core Lab

No pre-specified hypotheses for secondary effectiveness endpoints. Secondary effectiveness endpoint rates presented descriptively.

Safety Endpoint

- Serious adverse events as adjudicated by the DSMB including:
  - Death
  - Life threatening adverse events
  - Inpatient hospitalization or prolongation of an ongoing hospital stay
  - Persistent or significant disability/incapacity
  - Medically significant events, including laboratory abnormalities

No pre-specified hypotheses for safety.
Safety event rates presented descriptively.

RESPECT Trial Results

980 Enrolled Subjects (ITT Population)

499 Randomized to the Device

481 Randomized to MM

Baseline Demographics – ITT Population

	Device (N=499)	MM (N=481)	p-value
Age, years	45.7 (9.7)	46.2 (10.0)	0.491
Time from qualifying stroke to randomization, days	130 (70)	130 (69)	0.891
Sex, male	268 (53.7%)	268 (55.7%)	0.564
NIHSS score	0.8 (1.8)	0.7 (1.6)	0.073
Barthel Index	98.9 (5.2)	99.7 (1.4)	0.046
mRS score	0.8 (0.8)	0.7 (0.8)	0.069

Continuous variables reported as n, mean (SD)
Categorical variables reported as n (%)

Baseline Medical History - ITT Population

Medical History	Device (N=499)	MM (N=481)	p-value
Stroke prior to qualifying stroke	53/498 (10.6%)	51/481 (10.6%)	1.000
TIA	58/499 (11.6%)	61/481 (12.7%)	0.626
CAD	19/499 (3.8%)	9/481 (1.9%)	0.084
Previous MI	5/499 (1.0%)	2/481 (0.4%)	0.452
CHF	3/499 (0.6%)	0/481 (0.0%)	0.249
COPD	4/499 (0.8%)	7/481 (1.5%)	0.377
DVT	20/499 (4.0%)	15/481 (3.1%)	0.494

Baseline Stroke Risk Factors - ITT Population

	Device (N=499)	MM (N=481)	p-value
Current Smoker	75/499 (15.0%)	55/481 (11.4%)	0.109
Former smoker	134/499 (26.9%)	143/481 (29.7%)	0.322
Diabetes mellitus	33/499 (6.6%)	41/481 (8.5%)	0.278
Hypercholesterolemia	200/499 (40.1%)	202/481 (42.0%)	0.696
Hypertension	160/499 (32.1%)	153/481 (31.8%)	0.945
Atrial fibrillation	0/453 (0.0%)	1/442 (0.2%)	0.494
Birth control/HRT	41/499 (8.2%)	51/481 (10.6%)	0.228
Migraine	195/499 (39.1%)	186/481 (38.7%)	0.948
Other risk factor	37/456 (8.1%)	40/443 (9.0%)	0.636

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*Includes dyslipidemia and hyperlipidemia. Data was not collected on the use of lipid lowering medications during follow-up

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Former smoker	134/499 (26.9%)	143/481 (29.7%)	0.322
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Risk Factors for Ischemic Stroke

Atherosclerotic and non-atherosclerotic risk factors for stroke common (balanced between treatment groups)

- HTN ≈30%
- Hyperlipidemia ≈40%
- Current or former smokers ≈40%
- Migraine ≈40%

Baseline Cardiac Rhythm Evaluation to Exclude Subjects With Atrial Fibrillation or Atrial Flutter

Testing	Device	MM
ECG	487/499 (97.6%)	467/481 (97.1%)
Holter	67/499 (13.4%)	75/481 (15.6%)

Both ECG and an a Holter monitor were performed in:

- 11.0% (55/499) of Device subjects
- 12.7% (61/481) of MM subjects.

Neuroimaging Confirmation of Qualifying Strokes

- Neurologist investigators at study sites determined subject eligibility for enrollment
- The protocol definition of stroke did not require neuroimaging at the time of the qualifying stroke if stroke symptoms lasted >24 hours

Neuroimaging Confirmation of Qualifying Strokes

- 82 subjects (8.4%) lacked neuroimaging confirmation of the qualifying stroke
- Rate of neuroimaging confirmation of the qualifying stroke (vs. confirmation based on symptoms alone) lower in the Device group vs. the MM group

MRI/CT visualized infarct of qualifying stroke	Device (N=499)	MM (N=481)	p-value
Yes	447/499 (89.6%)	451/481 (93.8%)	0.021
No	52/499 (10.4%)	30/481 (6.2%)	

Neuroimaging Confirmation of Qualifying Strokes

MRI performed in 968 subjects

- MRI negative for acute infarct in 67 (6.9%) subjects

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Qualifying stroke	Device n (%)	MM n (%)
MRI negative	41/499 (8.3%)	26/481 (5.4%)
MRI performed ≤3 hrs of qualifying stroke	1/499 (0.2%)	0 (0%)
MRI performed ≥10 days post-qualifying stroke	7/499 (1.4%) Mean: 73±80 days Range: 22 – 242 days	6/481 (1.3%) Mean: 45.5±29.4 days Range: 11 – 82 days

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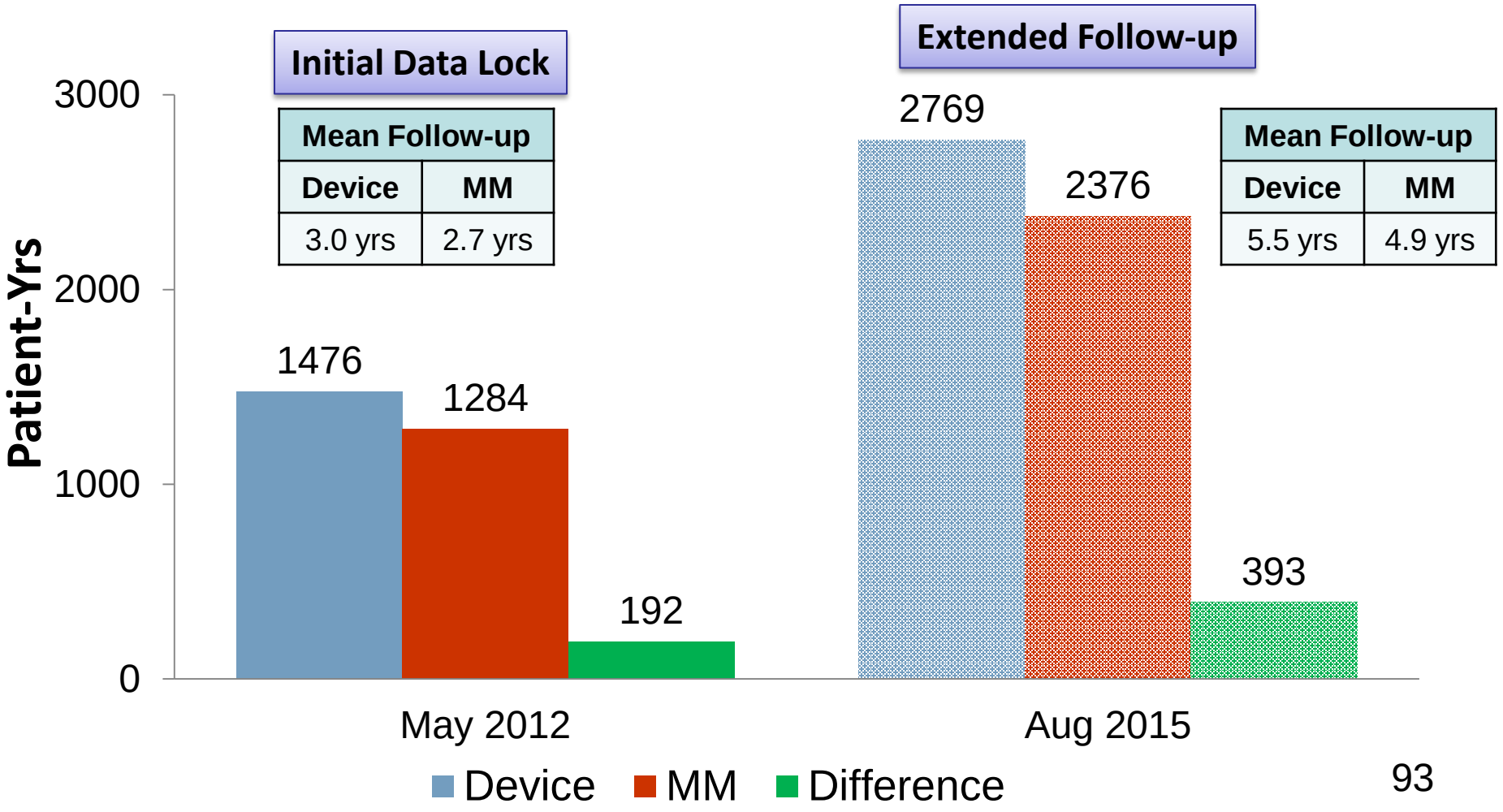
MRI performed ≥10 days post-qualifying stroke	7/499 (1.4%) Mean: 73±80 days Range: 22 – 242 days	6/481 (1.3%) Mean: 45.5±29.4 days Range: 11 – 82 days

Among subjects with no MRI performed, a CT scan performed ≥2 days post-stroke did not show an infarct in 5 Device subjects and 2 MM subjects

Concerns Regarding Cryptogenic Stroke Determination

- Investigations to exclude subjects with atrial fibrillation or atrial flutter limited in scope
- 8.1% of RESPECT subjects did not have MRI or CT confirmation of their qualifying stroke
  - Observed rate numerically higher in the Device group (10.4%) vs. the MM group (6.2%)
- Brain MRIs did not show an acute infarct in 6.9% of subjects in which an MRI was performed
  - Observed rate numerically higher rate in the Device group (8.3%) vs. the MM group (5.4%)

Subject Follow-up at Data Locks
ITT population



Unbalanced Subject Study Discontinuation

Subjects were discontinued if they withdrew consent, were lost-to-follow-up, died, or were withdrawn per the investigator

Disposition	Initial PMA Data Lock 20 May 2012		Extended Follow-up Data Lock 14 Aug 2015	
	Device (N=499)	MM (N=481)	Device (N=499)	MM (N=481)
Ongoing	447/499 (89.6%)	389/481 (80.9%)	408/499 (81.8%)	336/481 (69.9%)
Discontinued	52/499 (10.4%)	92/481 (19.1%)	91/499 (18.2%)	145/481 (30.1%)
Death	3/499 (0.6%)	6/481 (1.2%)	6/499 (1.2%)	10/481 (2.1%)
Withdrew consent	24/499 (4.8%)	55/481 (11.4%)	31/499 (6.2%)	71/481 (14.8%)
Lost to follow-up	22/499 (4.4%)	28/481 (5.8%)	50/499 (10.0%)	59/481 (12.3%)
Investigator request	3/499 (0.6%)	3/481 (0.6%)	3/499 (0.6%)	4/481 (0.8%)
Other	0/0 (0.0%)	0/0 (0.0%)	1/499 (0.2%)	1/481 (0.2%)

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Other	0/0 (0.0%)	0/0 (0.0%)	1/499 (0.2%)	1/481 (0.2%)

Unbalanced Subject Study Discontinuation

Higher discontinuation rate in the MM group driven by subjects deciding to withdraw from study participation.

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Investigator request	3/499 (0.6%)	3/481 (0.6%)	3/499 (0.6%)	4/481 (0.8%)
Other	0/0 (0.0%)	0/0 (0.0%)	1/499 (0.2%)	1/481 (0.2%)

Primary Effectiveness Endpoint Results

Primary Endpoint – Raw Count Analysis
ITT Population
Pre-Specified Primary Analysis

Initial Data Lock – Enrollment Stopped at 25 Events

All events were recurrent nonfatal ischemic strokes

	Device	MM
Subjects	499	481
Events n (%)	9 (1.80%)	16 (3.33%)
P-value	0.16	
Relative Risk (95% CI)	0.53 (0.23, 1.22)	

Primary Endpoint – Raw Count Analysis
ITT Population
Pre-Specified Primary Analysis

Extended Follow-up Data Lock

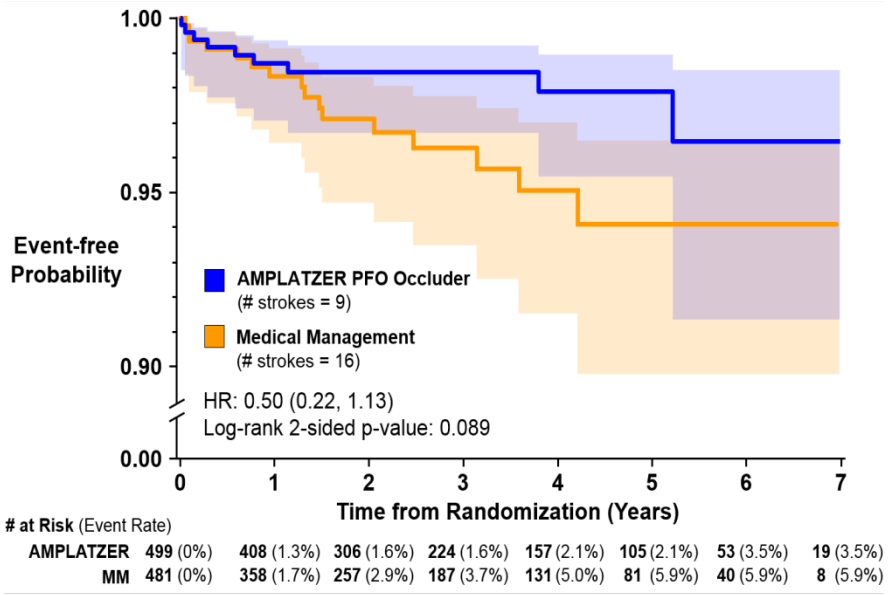
All events were recurrent nonfatal ischemic strokes

	Device	MM
Subjects	499	481
Additional events since the Initial Data Lock	9	8
Total Events n (%)	18 (3.61%)	24 (4.99%)

Primary Endpoint – ITT Population

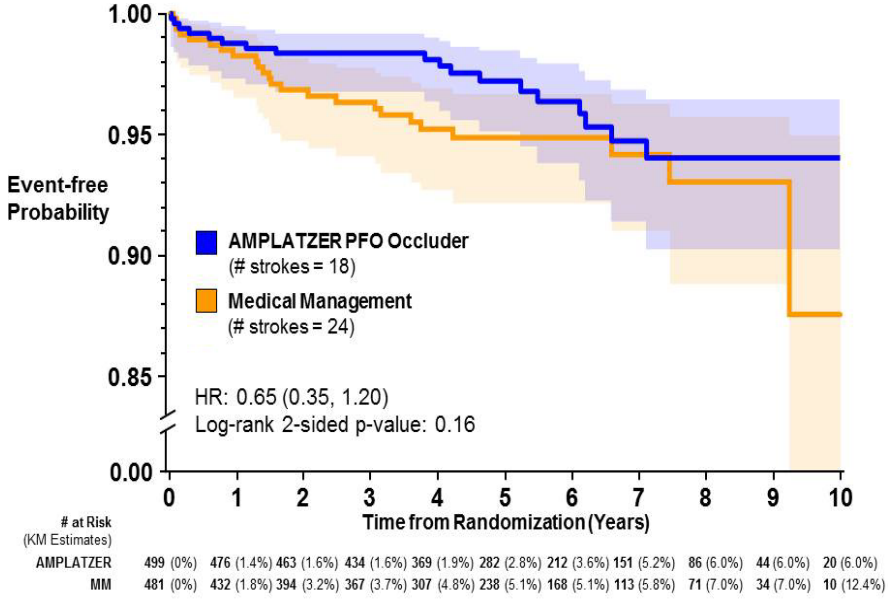
Initial Data Lock

Rate per 100 pt-yrs	
Device	**MM**
0.61	1.25



Extended Follow-up

Rate per 100 pt-yrs	
Device	**MM**
0.65	1.01



Anti-Thrombotic Therapy in the Week Prior to Recurrent Stroke

Extended Follow-up Data Lock

42 subjects with a primary endpoint event

- 39 subjects with medication information
  - 30 subjects were taking protocol-required medical therapy at the time of the recurrent event
    - 16 Device subjects and 14 MM subjects
  - 9 subjects were not using protocol-required medications in the week prior to their recurrent event
    - 2 Device subjects and 7 MM subjects

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Extended Follow-up Data Lock

42 subjects with a primary endpoint event

- 39 subjects with medication information
  - 30 subjects were taking protocol-required medical therapy at the time of the recurrent event
    - 16 Device subjects and 14 MM subjects
  - 9 subjects were not using protocol-required medications in the week prior to their recurrent event
    - 2 Device subjects and 7 MM subjects

Numbers too small to draw conclusions

Primary Effectiveness Endpoint Primary Analysis Considerations

In evaluating evidence supporting PFO closure with the Device closure to reduce the risk of recurrent stroke, one should consider of the small number of events relative to the number of subject withdrawals (and the differential dropout of subjects between treatment groups).

	Initial Data Lock		Extended Follow-up	
	Device	**MM**	**Device**	**MM**
Events	9 ↑	16 ↑	18	24
Subject Withdrawals*	49 ↓	86 ↓	84	134

***Excludes subjects who died or experienced a primary endpoint event**

Primary Effectiveness Endpoint - Primary Analysis Considerations

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	Initial Data Lock		Extended Follow-up	
	Device	**MM**	**Device**	**MM**
Events	9	16	18	24
Subject Withdrawals*	49	86	84	134

***Excludes subjects who died or experienced a primary endpoint event**

Primary Effectiveness Endpoint ITT Population

- The primary analysis was based on a small number of events (n=25) in the initial data lock.
- The primary endpoint of a lower recurrent stroke rate in the Device vs. the MM group based on the pre-specified ITT population raw count analysis was *not* met.

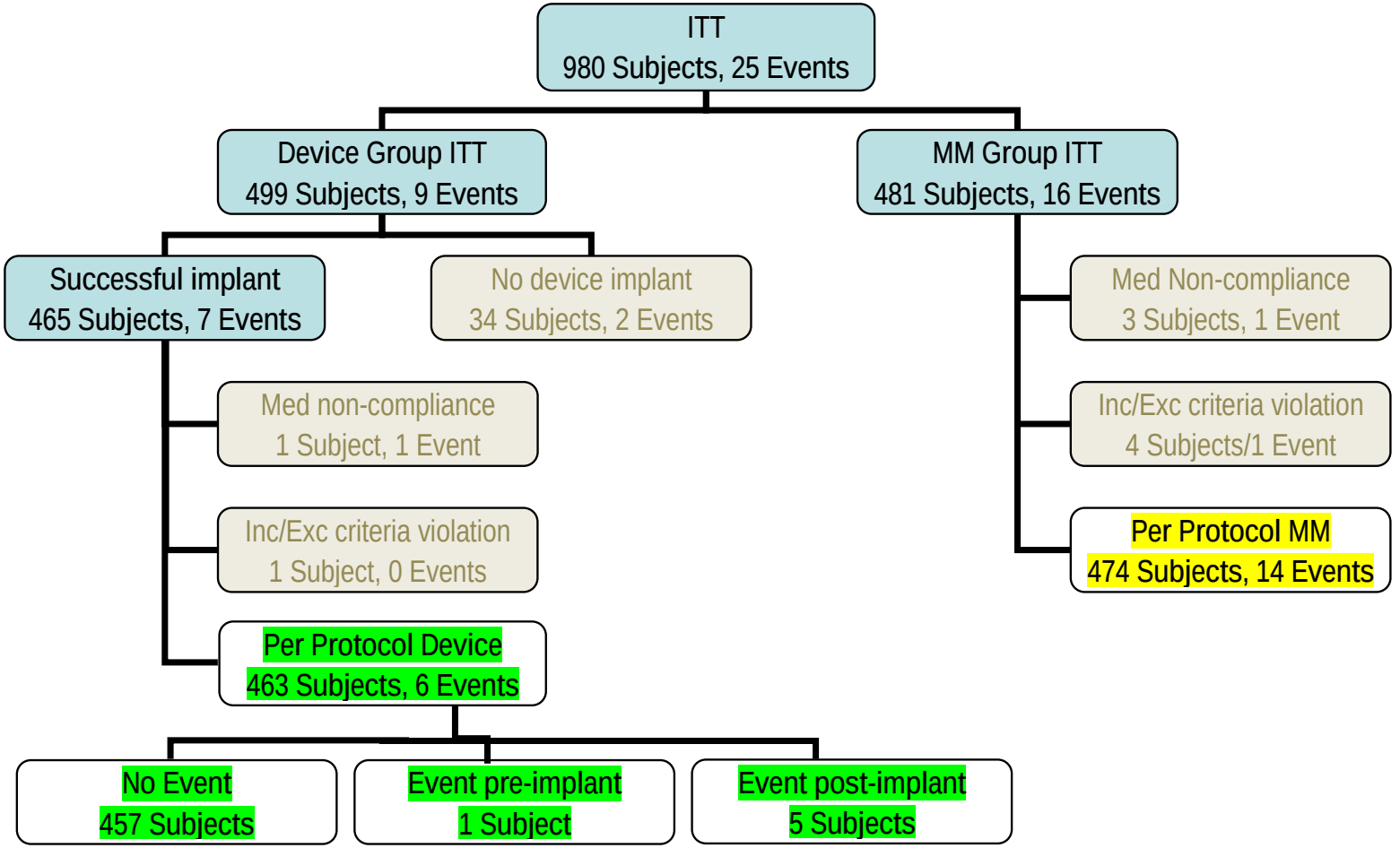
Primary Effectiveness Endpoint Supplementary Analyses – ITT population

- Event rates per patient year follow-up and Kaplan-Meier estimates:
  - Observed event rates per 100 pt-yrs in both treatment groups were small and numerically favored the Device group
  - K-M curves separate at around 1.5 years with overlapping 95% CIs, a wide CI around the HR, and a non-significant p-value
  - With extended follow-up, event rate differences narrow, and the K-M curves approach each other

Subject Withdrawals

- >5-fold higher than the number of events in both data locks
  - Disproportionally higher in the MM group
- Substantial missing data can lead to challenges in the interpretation of study results
- Imputation methods can help but cannot fully address uncertainty regarding the strength of the evidence

Subject Accountability – Per Protocol Population



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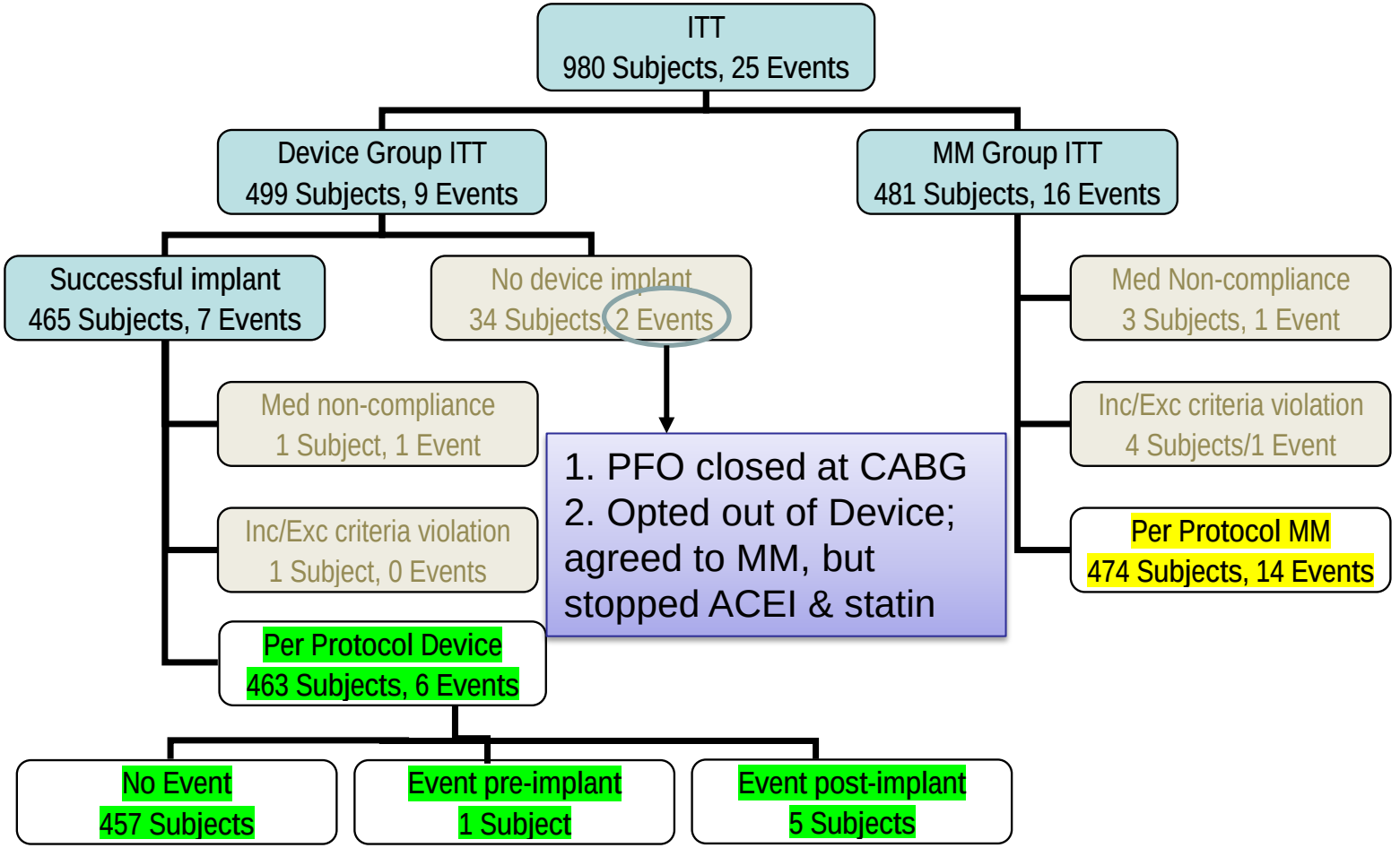

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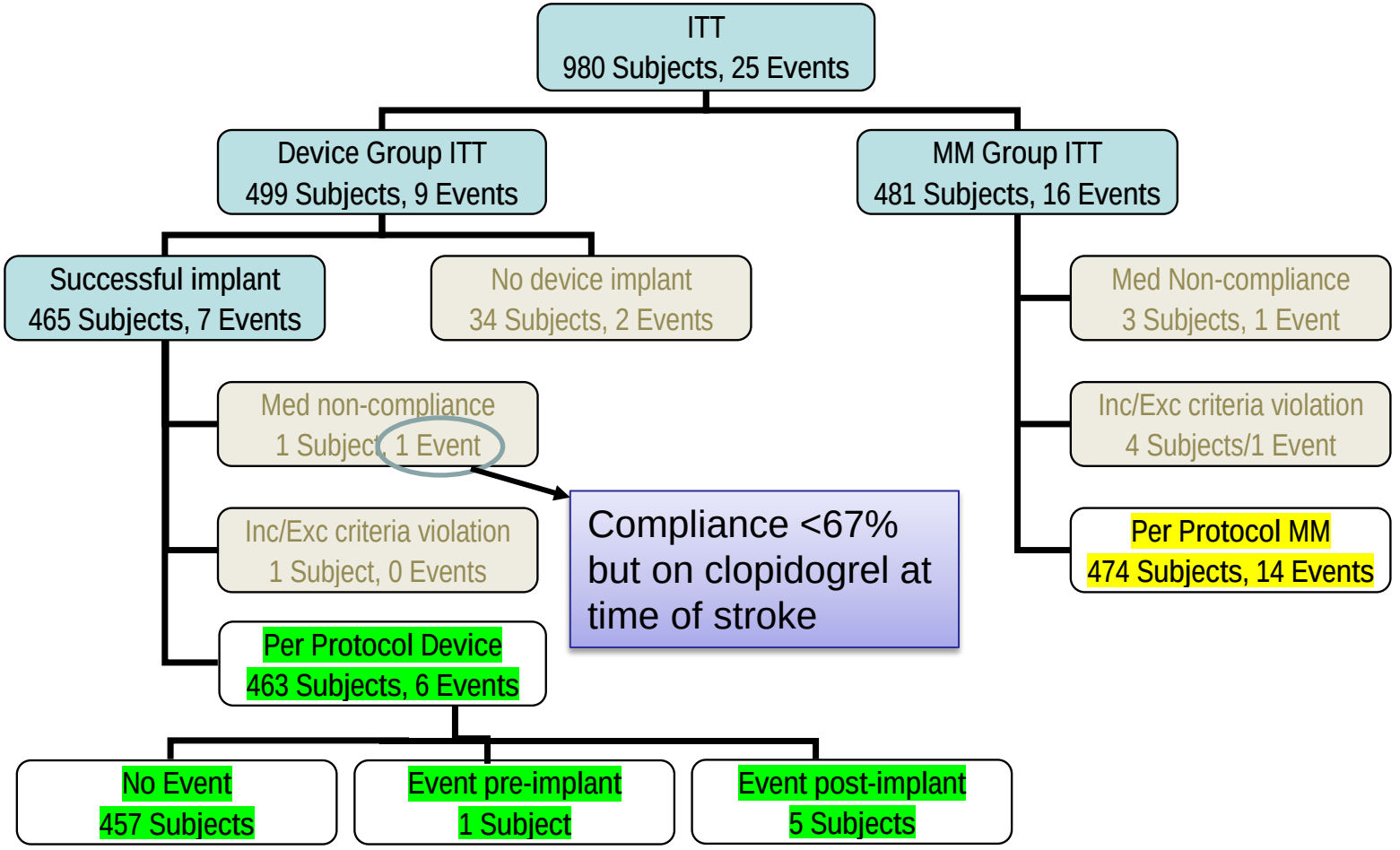

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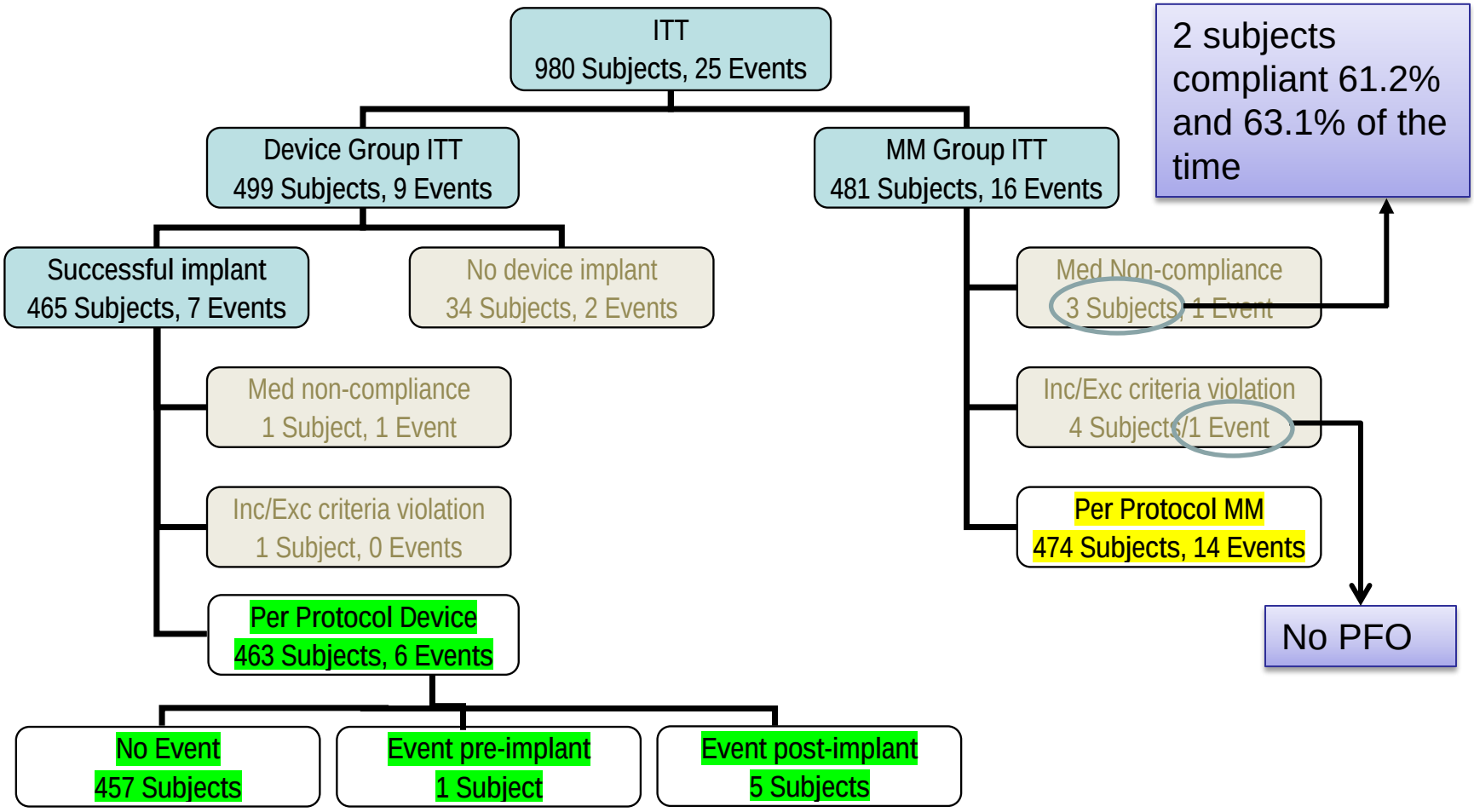


Per Protocol vs. ITT Subjects

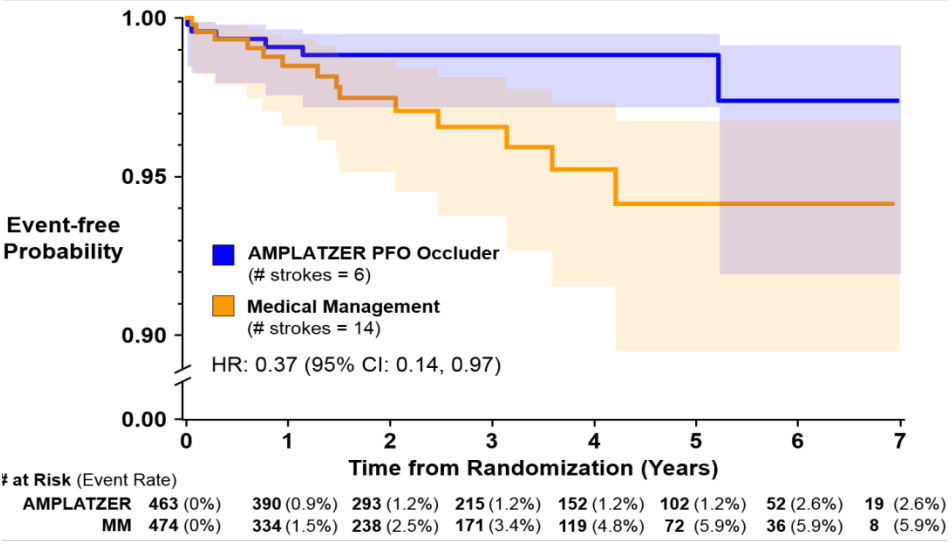
34 ITT Device subjects excluded from the Per Protocol analysis – No Device Implanted

- 17 subjects excluded based on evaluations or treatments performed *at the time of the implant procedure*:
  - PFO not confirmed or crossed or unsuccessful implant (n=8)
  - Atrial fibrillation observed at time of implant procedure (n=1)
  - Another source of right-to-left shunting identified (n=3)
  - Non-PFO Device or ASD found (n=4)
  - Significant coronary artery disease identified at the time of implant procedure; PFO closed surgically at the time of coronary artery bypass surgery (n=1)
- 12 subjects decided not to have the Device implanted
- 5 subjects with miscellaneous reasons

Primary Endpoint – Per Protocol Population

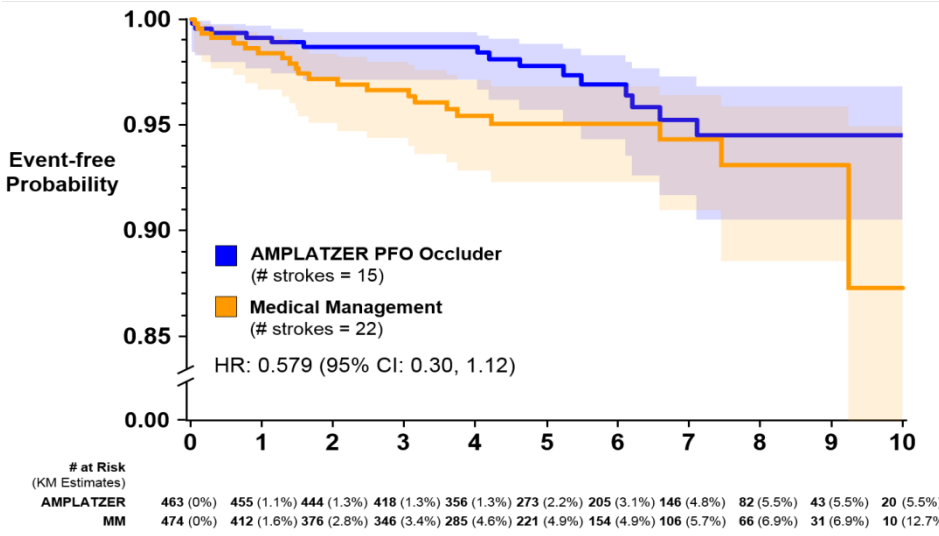
Initial Data Lock

Rate per 100 pt-yrs	
Device	**MM**
0.42	1.19

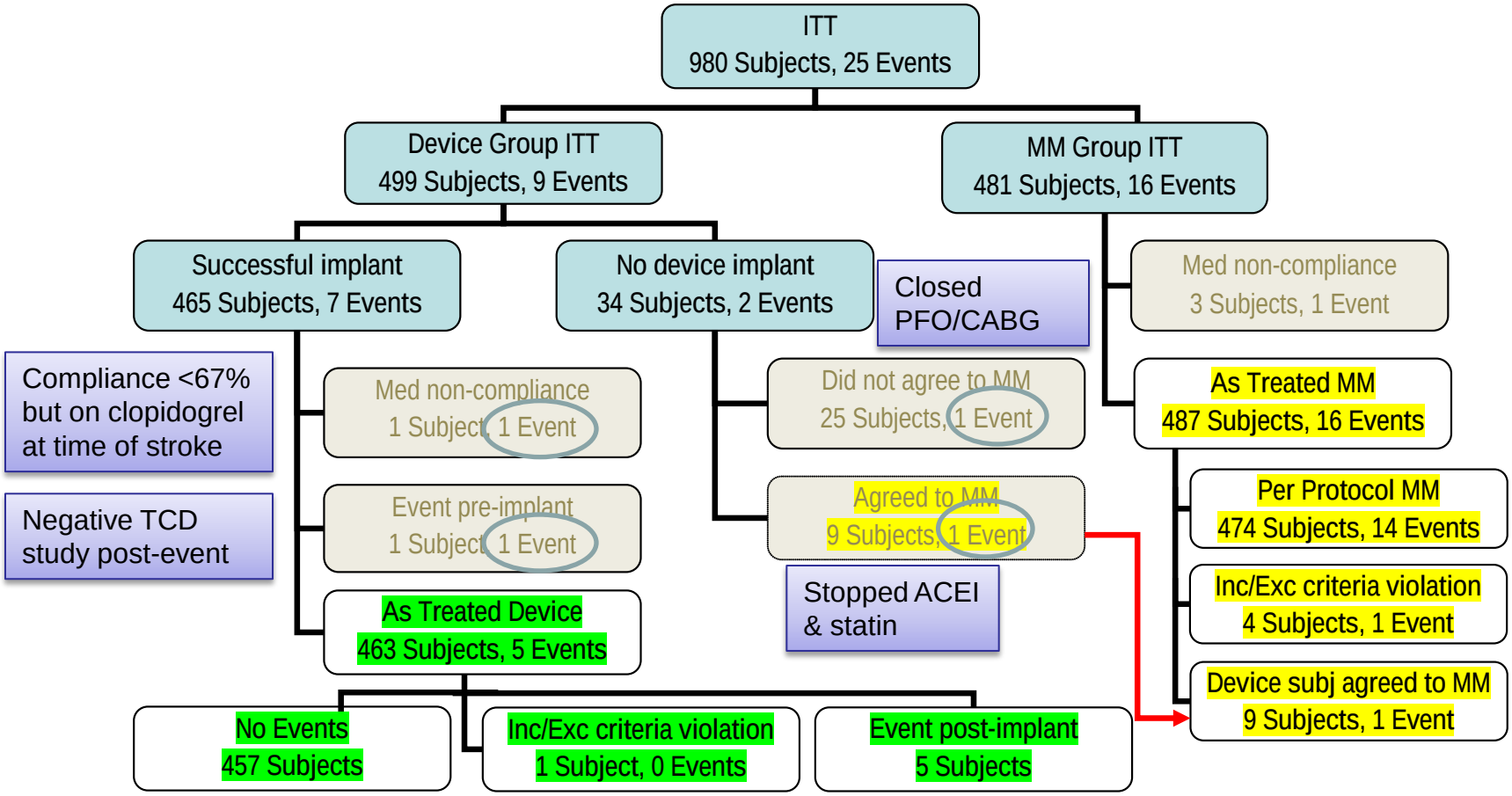


Extended Follow-up

Rate per 100 pt-yrs	
Device	**MM**
0.57	0.99



Subject Accountability - As Treated Population



As Treated vs. ITT Subjects

34 ITT Device subjects excluded from the Device group As Treated analysis – No Device Implanted

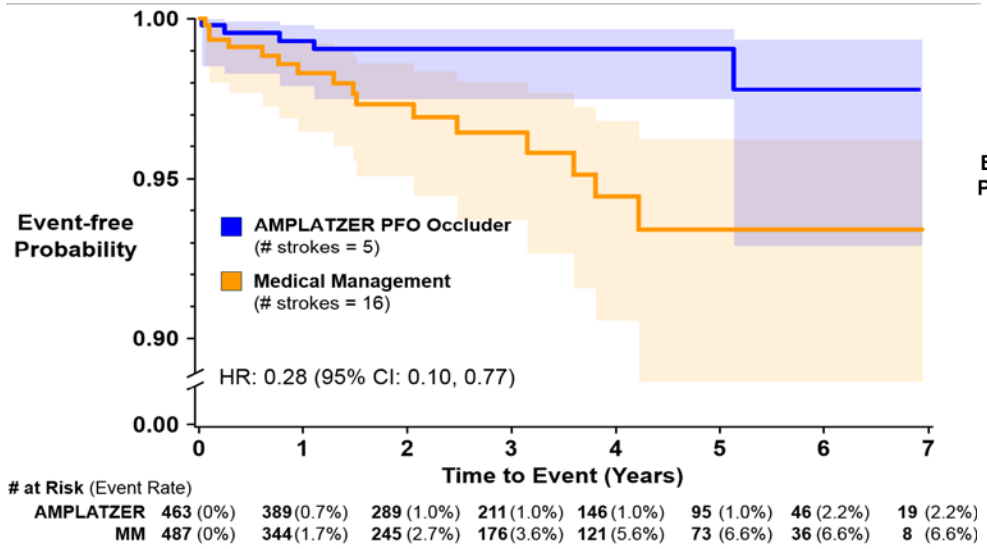
- 11 subjects excluded based on evaluations or treatments performed *at the time of the implant procedure*:
  - PFO not confirmed or crossed or unsuccessful implant (n=3)
  - Atrial fibrillation observed at time of implant procedure (n=1)
  - Another source of right-to-left shunting identified (n=2)
  - Non-PFO Device or ASD found (n=4)
  - Significant coronary artery disease identified at the time of implant procedure; PFO closed surgically at the time of coronary artery bypass surgery (n=1)
- 10 subjects decided not to have the Device implanted
- 4 subjects with miscellaneous reasons

9 subjects agreed to crossover to MM

Primary Endpoint – As Treated Population

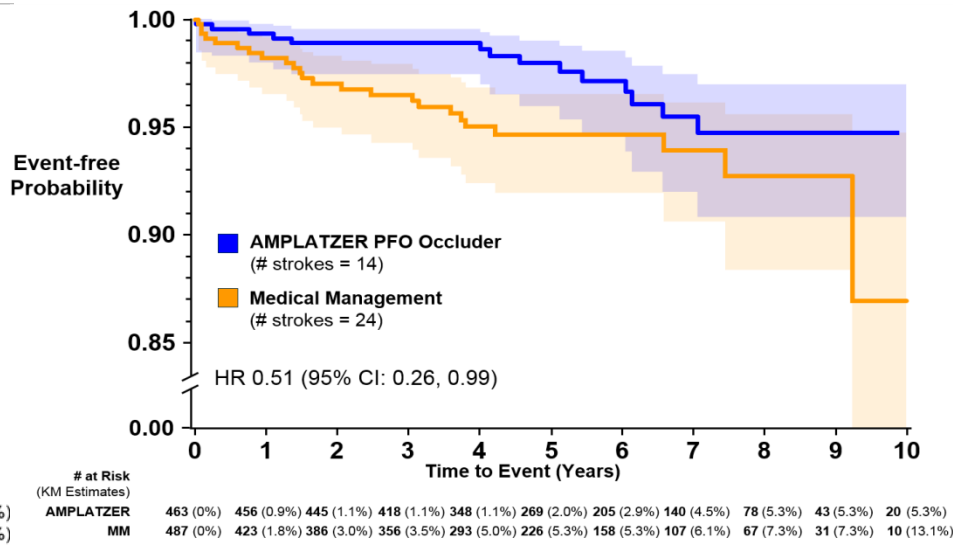
Initial Data Lock

Rate per 100 pt-yrs	
Device	**MM**
0.36	1.33

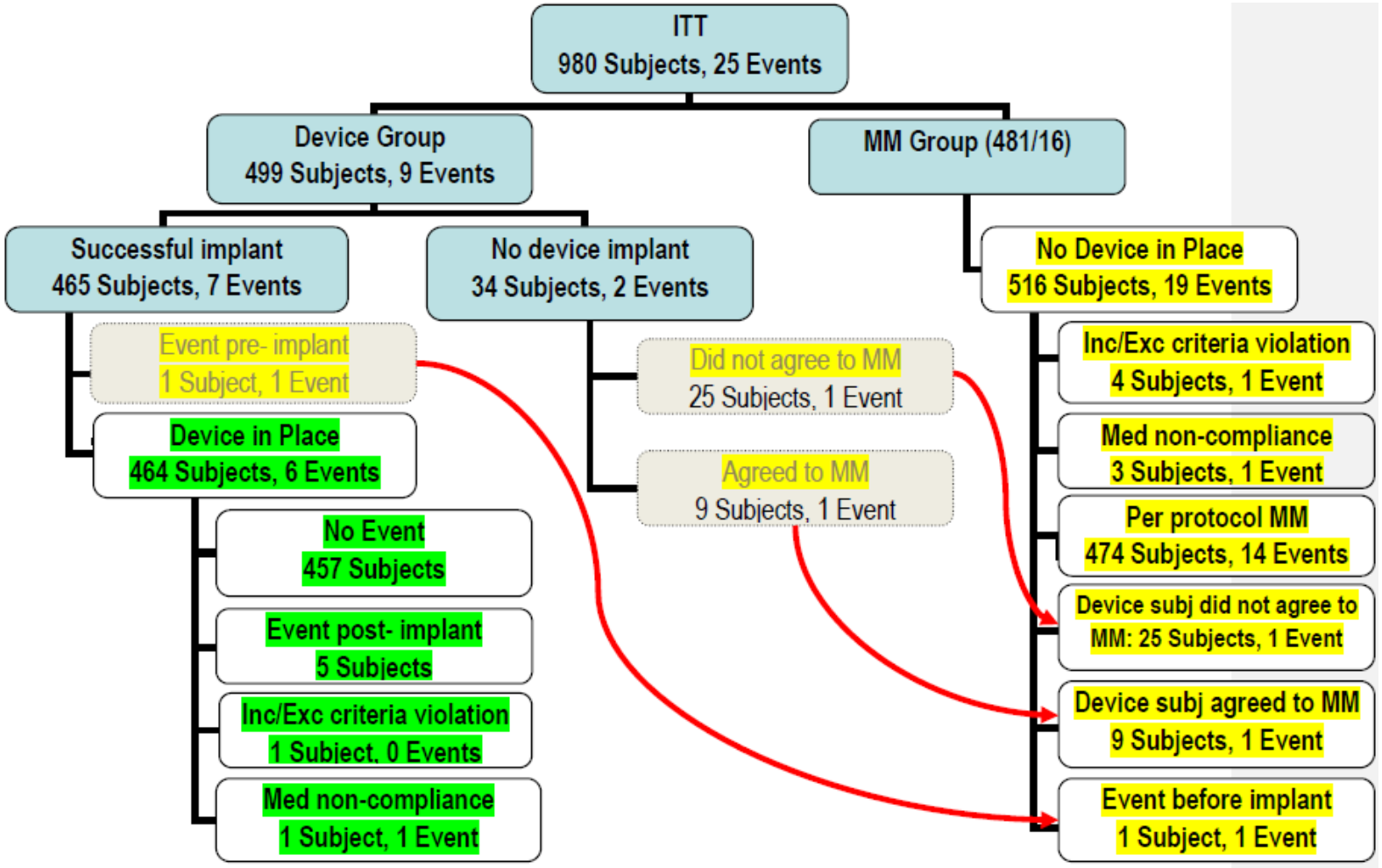


Extended Follow-up

Rate per 100 pt-yrs	
Device	**MM**
0.53	1.06



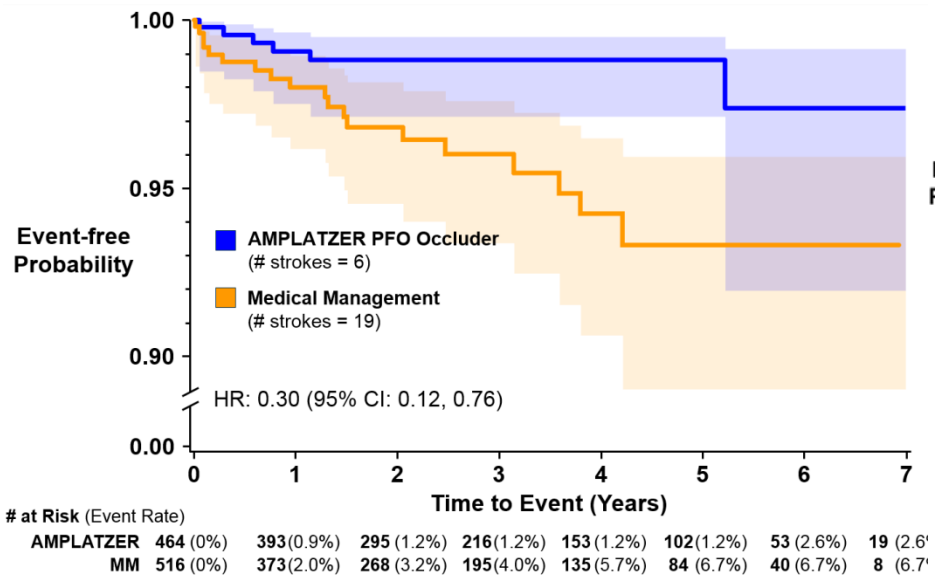
Subject Accountability – Device in Place Population



Primary Endpoint – Device in Place

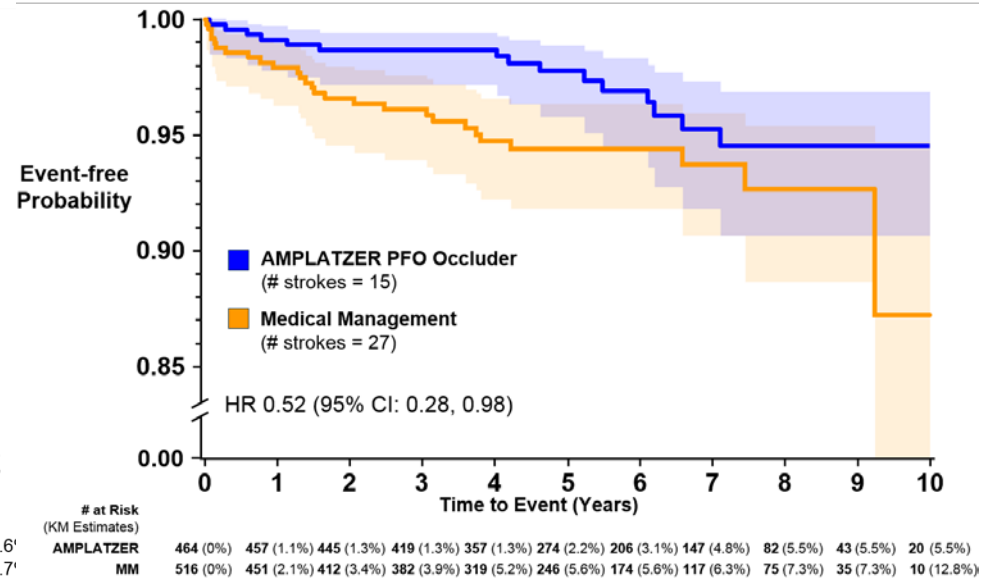
Initial Data Lock

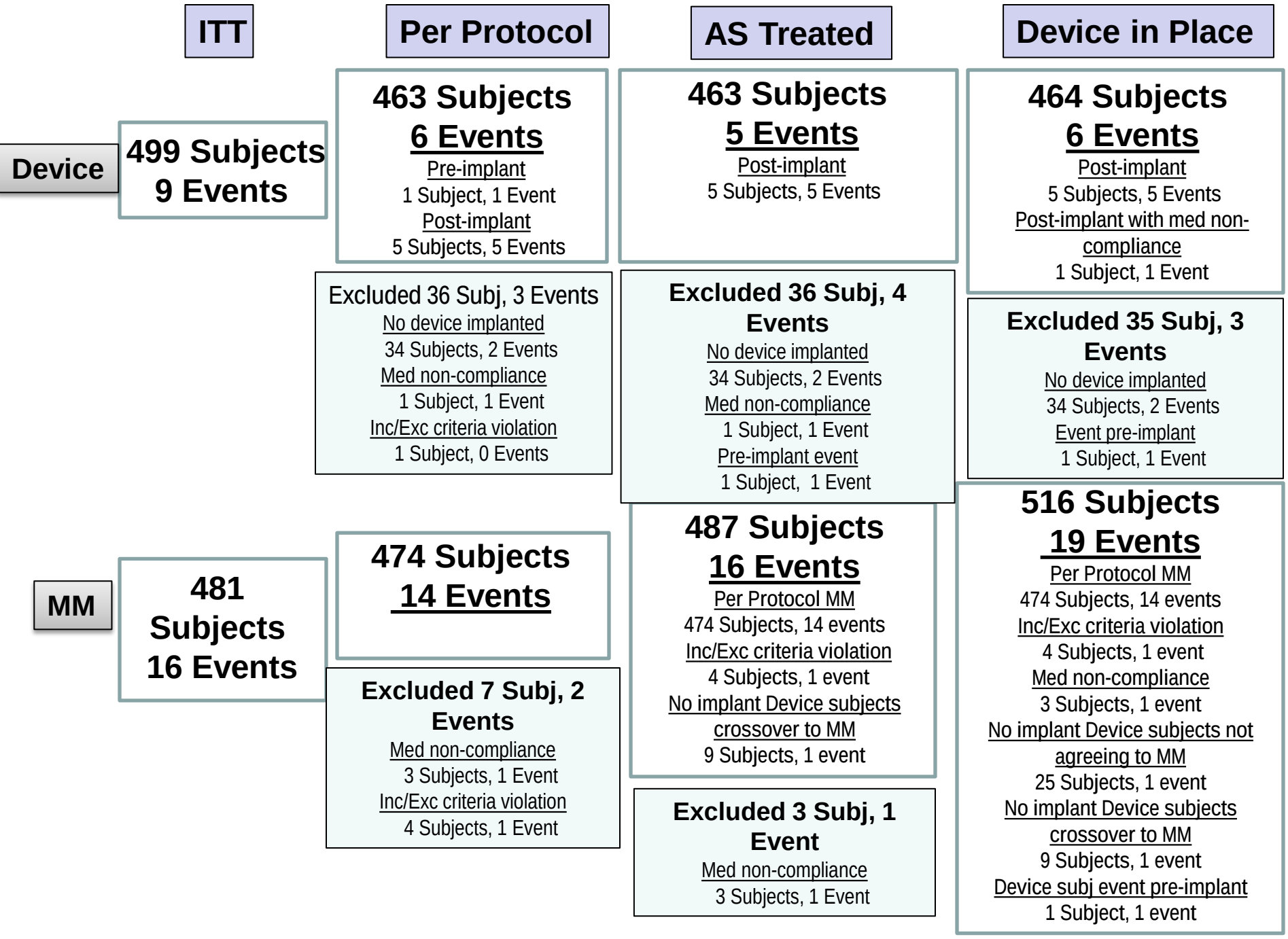
Rate per 100 pt-yrs	
Device	**MM**
0.42	1.41



Extended Follow-up

Rate per 100 pt-yrs	
Device	**MM**
0.56	1.09




ITT
Per Protocol
AS Treated
Device in Place
Device
499 Subjects
9 Events
463 Subjects
6 Events
Pre-implant
1 Subject, 1 Event
Post-implant
5 Subjects, 5 Events
463 Subjects
5 Events
Post-implant
5 Subjects, 5 Events
464 Subjects
6 Events
Post-implant
5 Subjects, 5 Events
Post-implant with med non-compliance
1 Subject, 1 Event
Excluded 36 Subj, 3 Events
No device implanted
34 Subjects, 2 Events
Med non-compliance
1 Subject, 1 Event
Inc/Exc criteria violation
1 Subject, 0 Events
Excluded 36 Subj, 4 Events
No device implanted
34 Subjects, 2 Events
Med non-compliance
1 Subject, 1 Event
Pre-implant event
1 Subject, 1 Event
Excluded 35 Subj, 3 Events
No device implanted
34 Subjects, 2 Events
Event pre-implant
1 Subject, 1 Event
MM
481 Subjects
16 Events
474 Subjects
14 Events
487 Subjects
16 Events
Per Protocol MM
474 Subjects, 14 events
Inc/Exc criteria violation
4 Subjects, 1 event
No implant Device subjects crossover to MM
9 Subjects, 1 event
516 Subjects
19 Events
Per Protocol MM
474 Subjects, 14 events
Inc/Exc criteria violation
4 Subjects, 1 event
Med non-compliance
3 Subjects, 1 event
No implant Device subjects not agreeing to MM
25 Subjects, 1 event
No implant Device subjects crossover to MM
9 Subjects, 1 event
Device subj event pre-implant
1 Subject, 1 event
Excluded 7 Subj, 2 Events
Med non-compliance
3 Subjects, 1 Event
Inc/Exc criteria violation
4 Subjects, 1 Event
Excluded 3 Subj, 1 Event
Med non-compliance
3 Subjects, 1 Event

Supplementary Analysis Populations

- Hazard ratios and p-values suggest a benefit of the Device vs. MM
- However:
  - Small number of events
  - Excluding and reassigning subjects can compromise the balance among measured and unmeasured baseline co-variates that is afforded by randomization
  - None of the p-values adjusted for multiplicity raising the possibility of false-positive results
  - Concerns regarding high and disproportionate number of subject withdrawals also apply to the interpretation of supplementary analysis populations

Insights from the Extended Follow-up Data Lock

With longer-term follow-up, as more patient-years and events accumulate, expected that the effect size of a durable treatment benefit would be maintained with a reduction in the upper bound of the 95% CI.

- However, compared to the initial data lock, extended follow-up analyses showed an increased hazard ratio and upper bound of the 95% CI for all analyses populations

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	ITT		Per Protocol		AS Treated		Device in Place	
	Initial Data Lock	Extended Follow-up	Initial Data Lock	Extended Follow-up	Initial Data Lock	Extended Follow-up	Initial Data Lock	Extended Follow-up
HR	0.50	0.64	0.37	0.58	0.28	0.51	0.30	0.52
Upper Bound 95% CI	1.13	1.20	0.97	1.12	0.77	0.99	0.76	0.98

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Number Needed to Treat – ITT Extended Follow-up Data Lock

	Time From Randomization (years)						
	0	**2**	**3**	**4**	**5**	**6**	**7**
Device Event Rate	0	0.0164	0.0164	0.019	0.0277	0.0362	0.0524
MM Event Rate	0	0.0316	0.0366	0.0478	0.0514	0.0514	0.0583
NNT		66	50	35	43	66	170

Number Needed to Treat – ITT Extended Follow-up Data Lock

	Time From Randomization (years)						
	0	**2**	**3**	**4**	**5**	**6**	**7**
Device Event Rate	0	0.0164	0.0164	0.019	0.0277	0.0362	0.0524
MM Event Rate	0	0.0316	0.0366	0.0478	0.0514	0.0514	0.0583
NNT		66	50	35	43	66	170

Stroke Mechanism During Extended Follow-up

The Sponsor's post-hoc ASCOD analysis suggests that PFO closure was associated with a reduction in the rate of recurrent strokes of undetermined mechanisms (i.e., fewer ASCOD Grade 1 strokes).

Post-Hoc ASCOD Phenotyping

Phenotype	Disease State
A	Atherosclerosis
S	Small vessel disease
C	Cardiac pathology
O	Other cause
D	Dissection

Grade	Underlying Disease
1	Disease present and potentially causal
2	Disease present and causal link is uncertain
3	Disease present and causal link is unlikely
0	Disease absent
9	Workup insufficient for grading

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Grade 1 stroke: Likely non-cryptogenic
Grade 0, 2, 3: Potentially cryptogenic?

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Grade 1 stroke: Likely non-cryptogenic
Grade 2, 3: Not Grade 1 ≠ Cryptogenic

Limitations of the ASCOD Grading Analysis

- ASCOD phenotyping developed to describe the degree of overlap among diseases known to cause ischemic stroke
  - Not designed to characterize stroke etiologies as cryptogenic (no *cryptogenic* phenotype in ASCOD)
- ASCOD not designed for *recurrent* strokes
- Insights based on ASCOD analysis of limited value
  - Standardized comprehensive evaluation of subjects to determine the etiology of the recurrent stroke lacking
  - ASCOD evaluation reported as incomplete for 11 events (4 Device, 7 MM), and in 6 additional events (3 Device, 3 MM), disease was present but link to the stroke was uncertain

Strokes in Subjects >60 Years Old

≤60 years of age – 34 strokes, 82% "undetermined" per ASCOD

>60 years of age – 8 strokes, 13% "undetermined" per ASCOD

- **New analysis, not previously reviewed by FDA**
- **Same limitations of the use of ASCOD grading apply to 60 years of age cutoff analysis (does not identify cryptogenic strokes)**

Totality of the Effectiveness Data

- High levels of subject discontinuation, particularly in the MM group, presents challenges to the interpretation of the effectiveness endpoint results.
- Although there were numerical trends for a reduced rate of recurrent stroke in favor of the Device, statistical significance for the primary endpoint in the ITT population (the primary analysis cohort) was not met.
- Observed event rates were more favorable to the Device group in the three supplementary analysis populations (Per Protocol, As Treated, Device in Place).
  - However, the robustness of these analyses are limited by potential bias associated with imbalances in baseline evaluations and switching treatment groups.

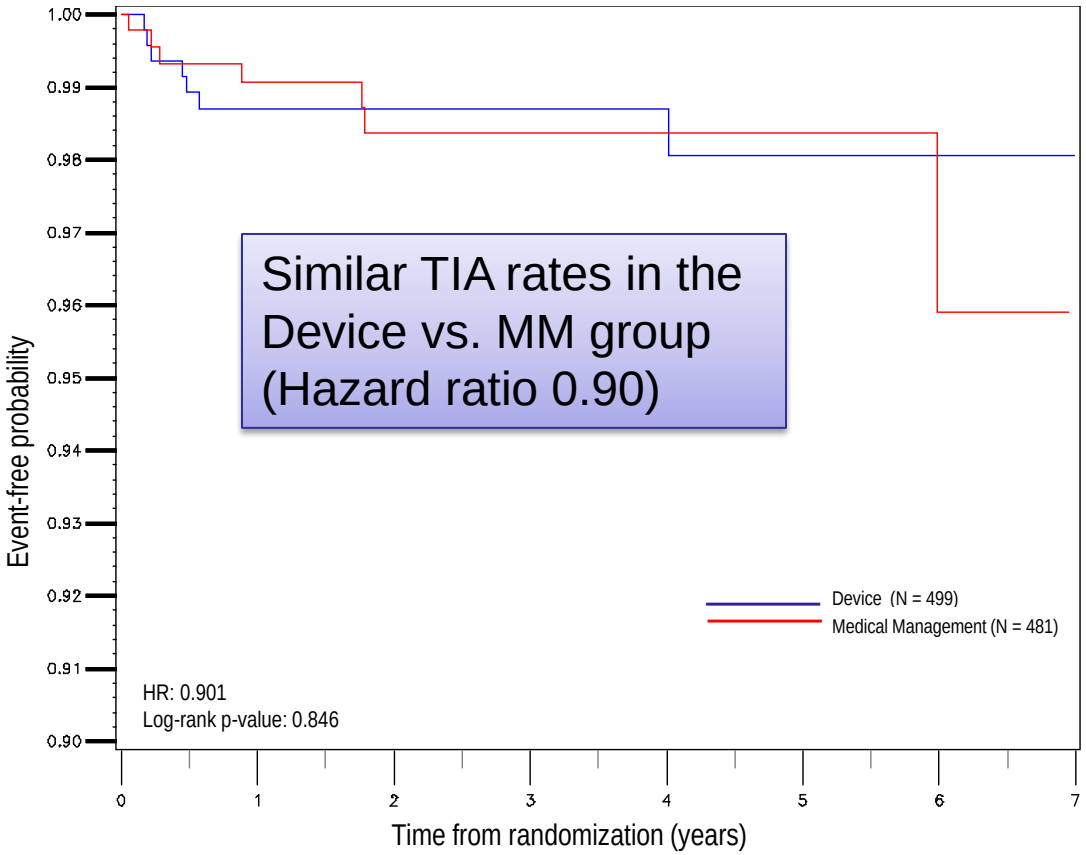
Totality of the Effectiveness Data

- The Sponsor's post-hoc ASCOD analysis suggests that PFO closure was associated with a reduction in the rate of recurrent strokes of undetermined mechanisms (i.e., fewer ASCOD Grade 1 strokes).
  - However, the scientific robustness of the ASCOD analysis is limited by the frequency of incomplete clinical assessments and the absence of a uniform evaluation process to determine the etiology of the recurrent stroke.

Secondary Effectiveness Endpoints

Secondary Endpoint – TIA
Initial Data Lock – ITT Analysis

Device	MM
7 events	7 events
Rate per 100 pt-yrs	
0.47	0.55



Secondary Endpoint – PFO Closure

465 Device subjects eligible for PFO closure analysis by 6 month TEE

- 349 subjects included in the PFO closure analysis
  - –338 subjects with both rest and Valsalva Echo Core Lab assessments
  - –11 subjects with a Grade 1 or higher shunt either at rest or with Valsalva included in the analysis as complete closure *failures*
- 116 subjects omitted from the analysis
  - –25 subjects did not undergo TEE
  - –TEE in 33 subjects had neither rest nor Valsalva results
  - –58 subjects with missing shunt grade assessment either at rest or with Valsalva

PFO closure data incomplete or missing in 116 (33.2%) subjects

Secondary Endpoint – PFO Closure

- *Complete* PFO closure rate at 6 months (pre-specified secondary endpoint)

Closure	Shunt grade	% (n/N)
Complete	Grade 0 at rest AND Grade 0 with Valsalva	71.3% (249/349)

Residual right-to-left shunting (incomplete closure) in 28.7% of assessed subjects

- *Effective* PFO closure rate at 6 months (supplementary analysis)

Closure	Shunt grade	% (n/N)
Effective	Grade 0 or I at rest AND Grade 0 or I with Valsalva	94.2% (323/343)

PFO Shunt Status in 18 Device Stroke Subjects

- 8 subjects - no shunt at rest and Valsalva
- 2 subjects - no shunt at rest (no Valsalva grade)
- 1 subject - grade I shunt at rest and Valsalva
- 2 subjects - no II shunt at rest and grade I or II with Valsalva
- 1 subject - shunting across a sinus venosus ASD
- 1 subject - shunt not classified
- 3 subjects - no Device at the time of the stroke
  - –1 subject - stroke post-randomization, prior to implant (Device implanted 1 week later)
  - –1 subject - opted out of implant but agreed to MM
  - –1 subject - found to have CAD (PFO closed at CABG)

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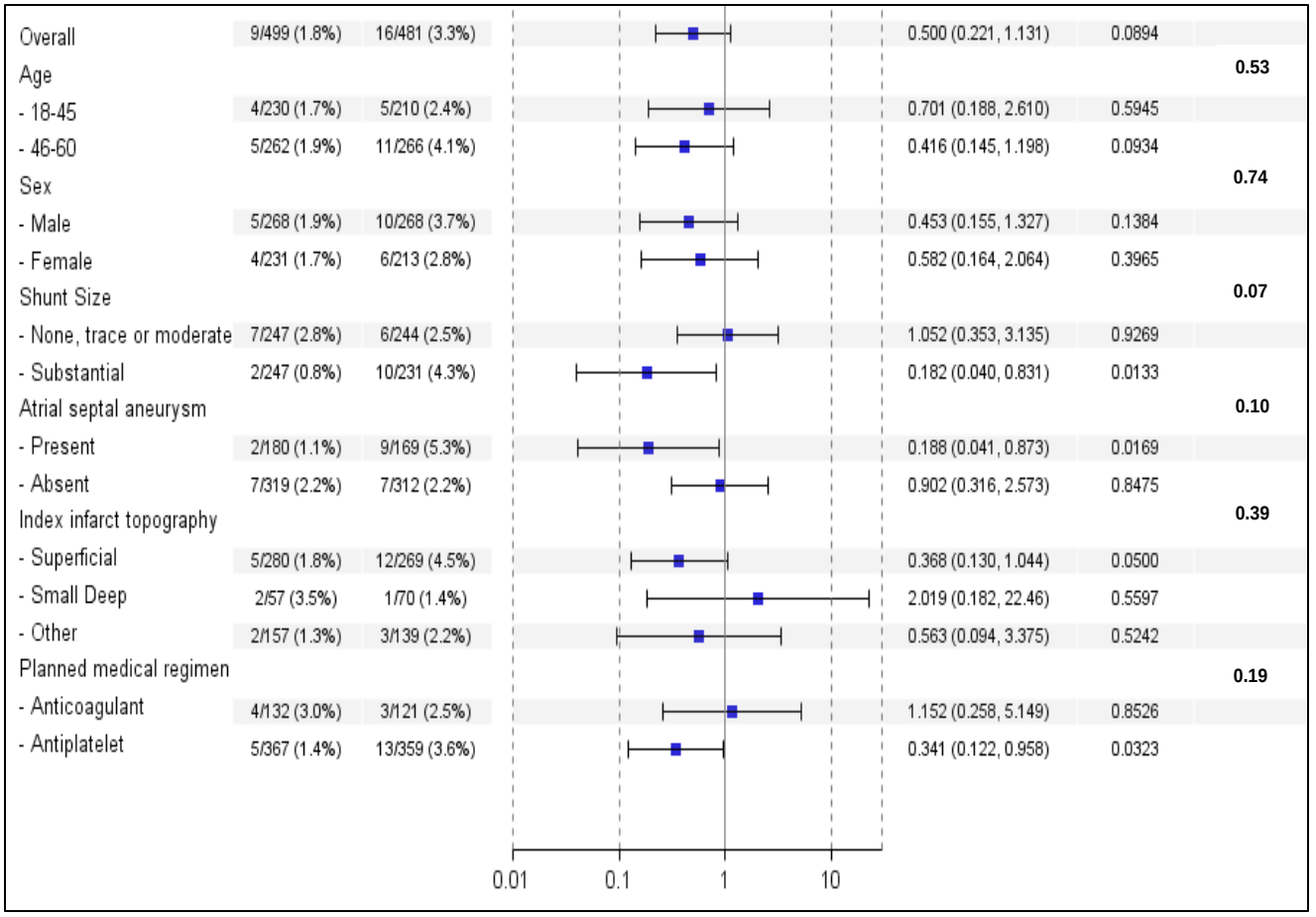
- **1 subject - grade I shunt at rest and Valsalva**
- **2 subjects - no II shunt at rest and grade I or II with Valsalva**
- 1 subject with shunting across a sinus venosus ASD
- [illegible]
- [illegible]
  - –1 subject with stroke post-randomization, prior to implant (Device implanted 1 week later)
  - –1 subject opted out of implant but agreed to MM
  - –1 subject found to have CAD - PFO closed at CABG

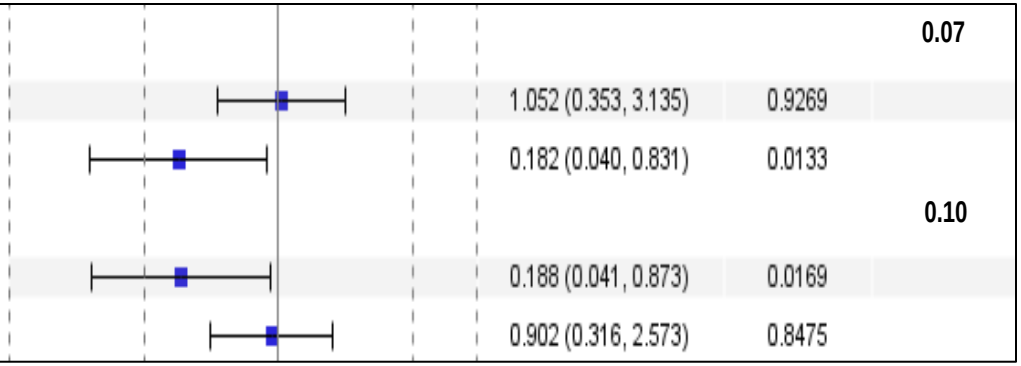
Residual right-to-left shunting (incomplete closure) present in 28.7% of assessed subjects

Subgroup Analysis of the Primary Endpoint ITT Population – Initial Data Lock



Subgroup Analysis of the Primary Endpoint ITT Population – Initial Data Lock

Shunt Size					0.07
- None, trace or moderate	7/247 (2.8%)	6/244 (2.5%)	1.052 (0.353, 3.135)	0.9269	
- Substantial	2/247 (0.8%)	10/231 (4.3%)	0.182 (0.040, 0.831)	0.0133	
Atrial septal aneurysm					0.10
- Present	2/180 (1.1%)	9/169 (5.3%)	0.188 (0.041, 0.873)	0.0169	
- Absent	7/319 (2.2%)	7/312 (2.2%)	0.902 (0.316, 2.573)	0.8475	



- The Device may provide an increased benefit in subjects with substantial shunt or an ASA
- Subgroup analyses should be considered as hypothesis-generating

Safety Assessments

Safety Assessment - Deaths

- 16 deaths: 6 in the Device group (6/499, 1.2%) and 10 in the MM group (10/481, 2.1%)
- None of the deaths were adjudicated as being related to the Device, procedure, delivery system, or study protocol.

Device Subjects (n=6)	**MM Subjects (N=10)**
Cancer, n=2	Cancer, n=3
Respiratory failure as a result of acute stroke/intracerebral hemorrhage, n=1	Intracerebral hemorrhage, n=1
Pulmonary embolism, n=1	Trauma, n=2
Asystole as a result of coronary artery disease, n=1	Cardiac arrest/dysrhythmia, n=3
Drug overdose (non-study medication), n=1	Sepsis, n=1

Device or Implant Procedure Serious Adverse Events (SAE's)

- 21 of 467 subjects with a Device implantation attempt (4.5%) had serious adverse events.
- No reported strokes resulting from air or observed thromboemboli from the device.

Selected Device or Implant Procedure Event	Subjects with Event	Event Rate
Ischemic stroke	2	0.4%
Pericardial tamponade	2	0.4%
Cardiac perforation	1	0.2%
Major vascular access site complication (bleeding or hematoma)	3	0.6%
Device explanted	2	0.4%

MM group SAEs Adjudicated as Protocol-Related

5 of 481 MM subjects (1.0%) had serious adverse events, which were adjudicated as related to the anti-thrombotic therapy

Event	Event Rate
Abnormal Lab Value	0.2% (1/481)
Hematoma	0.2% (1/481)
Menorrhagia	0.2% (1/481)
Subdural Hemorrhage	0.4% (2/481)

Safety Assessment – Major Bleeding

Device (N=499 subjects, 2769 pt-yrs)			MM (N=481 subjects, 2376 pt-yrs)		
Subjects	**Events**	**Event Rate (per 100 pt-yrs)**	**Subjects**	**Events**	**Event Rate (per 100 pt-yrs)**
13	17	0.61	14	14	0.59

Overall major bleeding rates similar between the Device and MM group

Rates of Supraventricular Arrhythmias

Event[a]	Device (N=499 subjects, 2769 pt-yrs)				MM (N=481 subjects, 2376 pt-yrs)			
	Subjects	Percent	Events	Rate (per 100 pt-yrs)	Subjects	Percent	Events	Rate (per 100 pt-yrs)
Atrial Fib	20	4.0%	23	0.83	9	1.9%	12	0.51
Atrial Flutter	2	0.4%	2	0.07	0	0.0%	0	0.00
PSVT	5	1.0%	5	0.18	0	0.0%	0	0.00

[a]Includes serious and non-serious adverse events

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Atrial Flutter	2	0.4%	2	0.07	0	0.0%	0	0.00
PSVT	5	1.0%	5	0.18	0	0.0%	0	0.00

[a]Includes serious and non-serious adverse events

Rates of DVT and PE

Event	Device (N=499 subjects, 2769 pt-yrs)				MM (N=481 subjects, 2376 pt-yrs)			
	Subjects	Percent	Events	Rate (per 100 pt-yrs)	Subjects	Percent	Events	Rate (per 100 pt-yrs)
DVT	11	2.2%	11	0.40	3	0.6%	3	0.13
PE	12	2.4%	13	0.47	2	0.4%	2	0.08
DVT or PE	18	3.6%	24	0.87	3	0.6%	5	0.21

Rates of DVT and PE

Event	Device (N=499 subjects, 2769 pt-yrs)				MM (N=481 subjects, 2376 pt-yrs)			
	Subjects	Percent	Events	Rate (per 100 pt-yrs)	Subjects	Percent	Events	Rate (per 100 pt-yrs)
DVT	11	2.2%	11	0.40	3	0.6%	3	0.13
PE	12	2.4%	13	0.47	2	0.4%	2	0.08
DVT or PE	18	3.6%	24	0.87	3	0.6%	5	0.21

Summary of Safety Assessment

- Subject deaths were uncommon, and there was no signal of increased mortality in either treatment group.
- The proportion of Device group subjects with SAEs related to the Device or implant procedure was 4.5%.
- Major bleeding rates were similar between treatment groups.
- The observed atrial fibrillation rate was numerically higher in the Device (4.0%) vs. the MM group (1.9%).
- There was a signal for a higher rate of deep venous thrombosis and pulmonary embolism in the Device vs. the MM group (3.6% vs. 0.6%, respectively).

Patient-Level Meta-Analysis

Pooled RESPECT and PC Trials

Meta-Analysis Limitations

- The analysis pools results from just 2 trials (RESPECT and PC) rather than aggregating data from many independent studies.
- The rates of multiple baseline patient characteristics, including those associated with ischemic stroke, differed between the PC and RESPECT trials.

Meta-Analysis: PC vs. RESPECT

	PC (n=414)		RESPECT (n=980)	
Diabetes	2.66% (11/414)		7.45% (73/980)	
Hypercholesterolemia	27.1% (112/414)		39.5% (387/980)	
HTN	25.8% (107/414		31.4% (308/980)	
Current smoker	23.9 (99/414)		13.3 (130/980)	
Migraine	20.5% (85/414)		38.8% (380/980)	
Prior stroke/TIA	37.4% (155/414)		18.6% (182/980)	
Hypermobile septum	23.7% (98/414)		35.6% (349/980)	
Large PFO	21.7% (80/369)		76.1% (737/969)	
Treated with antiplatelets only	80.0% (331/414)		88.0% (816/927)	
	Device	**MM**	**Device***	**MM***
Patient-years follow-up	845	835	1476	1284

***Initial data lock**

Other Meta-Analysis Limitations

- High rates of patient withdrawal and loss-to-follow-up (relative to the number of events) are more frequent in the MM group
  - Unascertained events may have impacted study outcomes
- Heterogeneous medical therapy regimens
- Did not include RESPECT extended follow-up data
  - Most patients were followed for approximately 2.5 years
- Authors of PC trial noted an imbalance in referral for endpoint adjudication
  - Events in Device group may have been less likely to be reported than events in the MM group

RESPECT and PC Trial Meta-Analysis

Other findings to consider

- Atrial fibrillation

Rate per 100 Pt-Yrs (ITT Population)		
Device	**MM**	**HR 95% CI**
0.93	0.48	1.94 (0.91 – 4.12)

- A large PFO or ASA did not identify patients likely to benefit from Device closure from those unlikely to benefit

Clinical Summary

- The RESPECT trial required a comprehensive assessment for causes of ischemic stroke (although the evaluation for fibrillation/atrial flutter had limitations).
  - It may be reasonable for conclusions drawn from RESPECT to be limited to the selected subgroup of patients with stroke and PFO in which known causes of ischemic stroke have been excluded by a neurologist and a cardiologist .

Clinical Summary - Effectiveness

- Initial data lock
  - Small number of events (n=25)
  - Low event rates
  - ITT population: Superiority of the Device vs. MM not demonstrated in either raw event count or Kaplan-Meier analyses

Clinical Summary - Effectiveness

- Initial data lock
  - Supplementary analysis population event rates more favorable in the Device group. However:
    - Excluding and re-assigning subjects can compromise balance in baseline co-variates afforded by randomization and impact on study outcomes difficult to predict
    - No adjustment in the p-values for multiplicity
  - High number of subject withdrawals (>5-fold higher than number of events) and unbalanced withdrawal (higher in the MM group) reduces the strength of the evidence.
    - Understandable in the context of the clinical landscape
    - Imputation methods helpful but do not fully address missing data concerns

Clinical Summary - Effectiveness

- Extended follow-up
  - High and unbalanced number of subject withdrawals
  - Increased hazard ratio (device vs. MM) and upper bound of the 95% CI for all analysis populations compared to the initial data despite more patient-year follow-up
    - Durable treatment effect provided by the Device?
  - Post-hoc ASCOD analysis to determine the likelihood of recurrent strokes to be more or less likely to be undetermined/cryptogenic:
    - Goes beyond the intended scope of ASCOD grading
    - Limited by incomplete clinical assessments and the absence of a standardized evaluation process

Clinical Summary
Major Secondary Endpoints

- No evidence that PFO closure reduces the TIA rate.
- Incomplete PFO closure common (28.7% of assessed subjects), and complete PFO closure assessment not available in 33.2% of subjects.

Clinical Summary – Safety

- The proportion of Device group subjects with serious adverse events related to the Device or implant procedure was 4.5%.
- Subject deaths and major bleeding events were uncommon, and no signal of differences between treatment groups observed.
- There were signals for an increased risk of atrial fibrillation and deep venous thrombosis/ pulmonary embolism in subjects treated with the Device that may warrant further investigation.

FDA Presentations

- Introduction and Regulatory History
  - Dr. Arielle Drummond
- Statistical Presentation
  - Dr. Rong Tang
- Clinical Presentation
  - Dr. Andrew Farb
- **Post-Approval Considerations**
  - **Dr. Erika Tang**
- Summary
  - Dr. Arielle Drummond

Post – Approval Considerations AMPLATZER PFO Occluder

Erika Tang, PhD
Division of Epidemiology
Office of Surveillance and Biometrics
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration

Reminder

- The discussion of a Post-Approval Study (PAS) prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective.
- The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate risk/benefit balance.

Post-market Conditions of Approval

- Additional non-clinical/bench testing
- Extended follow-up of premarket cohort
- New patient data collection to address focused benefit-risk questions and/or evaluation of operator training programs
  - Stand-alone post-approval study
  - Comprehensive registry-based surveillance with shared responsibilities

Postmarket Issues Specific to the Amplatzer PFO Occluder

- Long-term safety and effectiveness of the device
  - Recurrent ischemic stroke
  - Device- or procedure-related serious adverse events (SAEs)
  - Deep venous thrombosis
  - Pulmonary embolism
  - Atrial arrhythmias
  - Complete PFO closure
- Evaluation of the training program for new operators

Sponsor's Proposed New Enrollment Post-Approval Study Plan

Study Design	Multi-center, single arm prospective cohort study
Objectives	▪ To demonstrate long-term safety of the Amplatzer PFO Occluder by assessing the rate of device- or procedure-related SAEs ▪ To demonstrate that the AMPLATZER PFO Occluder is effective by assessing the rate of recurrent ischemic stroke

Sponsor's Proposed PAS Plan (Cont.)

Primary Effectiveness Endpoint and Hypothesis	The 5-year rate of the composite of: ▪ recurrent non-fatal ischemic stroke ▪ fatal ischemic stroke Hypothesis test: H_0: p ≥4.4% H_1: p <4.4% where p = proportion of patients experiencing a primary effectiveness endpoint event

Sponsor's Proposed PAS Plan (Cont.)

Primary Safety Endpoint and Hypothesis	The 5-year rate of the composite of device- or procedure-related SAEs including: ▪ New onset atrial fibrillation ▪ Pulmonary embolism ▪ Device thrombus ▪ Device erosion/embolization ▪ Major bleeding requiring transfusion ▪ Vascular access site complications requiring surgery ▪ Device- or procedure-related SAE leading to death Hypothesis test: H_0: p ≥4.0% H_1: p <4.0% where p = proportion of patients experiencing a device- or procedure-related SAE

Sponsor's Proposed PAS Plan (Cont.)

Descriptive Endpoints	▪ Components of primary effectiveness endpoint ▪ All-cause mortality ▪ Transient Ischemic Attack (TIA) ▪ Effective PFO closure at 1 year ▪ Technical success ▪ Procedural success
Sample Size	806 subjects (~80 US sites)
Length of Follow-up	Follow-up of 5 years ▪ Clinical follow-up at 1, 6, and 12 months ▪ Telephone follow-up annually years 2-5

FDA Assessment of PAS Plan

- Primary endpoints and five years length of follow-up are reasonable
- Assessment of additional endpoints:
  - Deep venous thrombosis and atrial arrhythmias
  - *Complete* PFO closure
- Evaluation of the training program for new operators
  - Technical/Procedural success
  - Procedure-related adverse events

Panel Input

The panel will be asked to provide input on

- the proposed post-approval study design
- additional elements or objectives

for the surveillance on the safety and effectiveness of the device.

FDA Presentations

- Introduction and Regulatory History
  - Dr. Arielle Drummond
- Statistical Presentation
  - Dr. Rong Tang
- Clinical Presentation
  - Dr. Andrew Farb
- Post-Approval Considerations
  - Dr. Erika Tang
- **Summary**
  - **Dr. Arielle Drummond**

FDA Summary

- Primary effectiveness endpoint was not met in ITT analysis
- Supplementary analyses is more favorable to the Device group for reducing the risk of ischemic stroke
  - Robustness of the results are limited
- Subject discontinuation rate was high in the trial and numerically higher in the MM vs. the Device group
  - Number of discontinued subjects was substantially higher than the number of subjects with recurrent ischemic stroke events
- Extended follow-up analyses demonstrate a smaller difference in recurrent ischemic stroke rates in the Device vs. MM groups

FDA Summary

- Observed rates of safety events (atrial fibrillation, deep venous thrombosis, pulmonary embolism) numerically higher in Device subjects
- PFO closure assessment at 6-month by TEE
  - Residual shunting was common, occurring in 28.7% of assessed subjects
  - Assessment data unavailable in approximately 25% of Device subjects

AMPLATZER PFO Occluder

FDA Review of P120021

Panel Questions

Question 1
Primary Effectiveness Endpoint

Table 1a. Primary endpoint outcomes in the ITT population

Device 499 Subjects/9 Events		**MM 481 Subjects/16 Events**		**Relative Risk[a] (D vs MM) (95% CI)**	**p-value[b]**
Pt-Yrs	Rate per 100 Pt-yrs	Pt-Yrs	Rate per 100 Pt-yrs		
1476	0.61	1284	1.25	0.50 (0.22, 1.13)	0.089

[a] The relative risk is represented by the hazard ratio [b] 2-sided p-value using log-rank test

Table 1b. Primary endpoint outcomes in the ITT population– extended follow-up

Device 499 Subjects/18 Events		**MM 481 Subjects/24 Events**		**Relative Risk[a] (D vs MM) (95% CI)**	**p-value[b]**
Pt-Yrs	Rate per 100 Pt-yrs	Pt-Yrs	Rate per 100 Pt-yrs		
2769	0.65	2376	1.01	0.65 (0.35, 1.20)	0.16

[a] The relative risk is represented by the hazard ratio [b] 2-sided p-value using log-rank test (unadjusted for multiplicity)

Question 1
Primary Effectiveness Endpoint

Please comment on the clinical significance of these results.

Question 2

Primary Endpoint Supplementary Analyses

Table 2: Initial PMA data lock and extended follow-up results

	Device Rate per 100 Pt-yrs	MM Rate per 100 Pt-yrs	Relative Risk[a] (D vs MM) (95% CI)
PP – Initial Data Lock	0.42	1.19	0.37 (0.14, 0.97)
PP – Extended Follow-up	0.57	0.99	0.58 (0.30, 1.12)
AT - Initial Data Lock	0.36	1.33	0.28 (0.10, 0.77)
AT - Extended Follow-up	0.53	1.06	0.51 (0.26, 0.99)
DIP - Initial Data Lock	0.42	1.41	0.30 (0.12, 0.76)
DIP - Extended Follow-up	0.56	1.09	0.52 (0.28, 0.94)

Question 2
Primary Endpoint Supplementary Analyses

- Limited robustness of the results of analyses
  - Extended follow-up demonstrate a smaller difference in recurrent ischemic stroke rates in the Device vs. MM group
  - Subject discontinuation rate high in trial and numerically greater in MM vs. the Device group
  - P-values reported were not adjusted for multiplicity, such that the probability of obtaining statistically significant results due to chance increases

Question 2
Primary Endpoint Additional Analyses

Please comment on the clinical significance of these results.

Question 3
Safety Events

Table 3a. Selected SAEs related to the Device or implantation procedure – Device group only

Selected Device or Implant Procedure Event	Subjects with Event	Event Rate
Ischemic stroke	2	0.4%
Pericardial tamponade	2	0.4%
Cardiac perforation	1	0.2%
Major vascular access site complication (bleeding or hematoma)	3	0.6%
Device explanted	2	0.4%

Question 3
Safety Events

Table 3b. Rates of atrial arrhythmias

Event	Device (N=499 subjects, 2769 patient-years)				MM (N=481 subjects, 2376 patient-years)			
	Subjects	Percent	Events	Rate (per 100 pt years)	Subjects	Percent	Events	Rate (per 100 pt years)
Atrial Fibrillation	20	4.0%	23	0.83	9	1.9%	0	0.51
Atrial Flutter	2	0.4%	2	0.07	0	0.0%	0	0.00
PSVT	5	1.0%	5	0.18	0	0.0%	0	0.00

Question 3
Safety Events

Table 3c. Rates of deep venous thrombosis and pulmonary embolism

Event	Device (N=499 subjects, 2769 patient-years)				MM (N=481 subjects, 2376 patient-years)			
	Subjects	Percent	Events	Rate (per 100 pt years)	Subjects	Percent	Events	Rate (per 100 pt years)
DVT or PE	18	3.6%	24	0.87	3	0.6%	5	0.21
DVT	11	2.2%	11	0.40	3	0.6%	3	0.13
PE	12	2.4%	13	0.47	2	0.4%	2	0.08

Question 3
Safety Events

Please comment on the safety profile of the Device, the clinical significance of the safety events, and the rates of safety events between the Device and MM groups.

Question 4
PFO Closure by the Device

Table 4. 6-month PFO closure data
Device group subjects who received a Device

Closure	Shunt grade	n/N (%)
Complete	Grade 0 Rest AND Grade 0 Valsalva	249/349 (71.3%)
Effective	Grade 0/I Rest AND Grade 0/I Valsalva	323/343 (94.2%)

Question 4
PFO Closure by the Device

Please comment on the rate of PFO closure by the Device.

Question 5
Proposed Indications for Use

The sponsor proposed the following Indications for Use:

"The AMPLATZER PFO Occluder is intended for percutaneous, transcatheter closure of a patent foramen ovale (PFO) to prevent recurrent ischemic stroke in patients who have had a cryptogenic stroke due to a presumed paradoxical embolism."

Please comment on this Indications for Use statement.

Question 6
Labeling

Please comment on whether the proposed labeling is acceptable or whether modifications are recommended.

Question 7
Benefit – Risk Assessment

The sponsor has presented data from the RESPECT trial, including an initial PMA data lock and an extended follow-up data lock. There were relatively few primary endpoint events (42 in total) in a trial that enrolled 980 subjects, with the vast majority of subjects followed for at least 4 to 5 years. The low number of recurrent strokes and the small event rate differences between treatment groups (0.65 per 100 patient years in the Device group vs. 1.01 per 100 years in the MM group in the extended follow-up ITT analysis) suggests that many patients could be potential candidates for an invasive cardiac procedure to implant a permanent device to prevent a relatively uncommon event (vs. medical therapy alone). There was no particular patient subgroup identified for whom there is strong evidence for an enhanced benefit associated with implantation of the Device.

Question 7
Benefit – Risk Assessment

Based on the data presented from the RESPECT trial, do the probable benefits of the AMPLATZER device outweigh the probable risks?

In answering this question, please comment on the topics on the next slides.

Question 7
Benefit – Risk Assessment

a. Whether the results of the RESPECT trial support an important role of the presence of a PFO in the pathophysiology of cryptogenic ischemic stroke.

b. Whether the results of the RESPECT trial provides compelling evidence that the Device provides a clinically meaningful reduction in the risk of recurrent ischemic stroke vs. medical therapy.

c. Whether the safety profile of the Device implantation procedure and the Device itself are acceptable in the context of the estimated reduction in the risk of recurrent ischemic stroke.

Question 8
Post-Approval Studies

Please comment on any additional study objectives or design features that you recommend for the post-approval study and whether or not the sponsor's post-approval commitments are acceptable.

Voting Questions

Proposed Indications for Use

Indications for Use:

The AMPLATZER PFO Occluder is intended for percutaneous, transcatheter closure of a patent foramen ovale (PFO) to prevent recurrent ischemic stroke in patients who have had a cryptogenic stroke due to a presumed paradoxical embolism.

Voting Question 1

Is there reasonable assurance that the AMPLATZER™ PFO Occluder is safe for patients who meet the criteria specified in the proposed indication?

Voting Question 2

Is there reasonable assurance that the AMPLATZER™ PFO Occluder is effective for use in patients who meet the criteria specified in the proposed indication?

Voting Question 3

Do the benefits of the AMPLATZER™ PFO Occluder outweigh the risks for use in patients who meet the criteria specified in the proposed indication?