Long-term Comparison of Patent Foramen Ovale (PFO) Closure versus Medical Therapy after Cryptogenic Stroke:

Final Results of the RESPECT Trial

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On Behalf of RESPECT Investigators

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	
• Consulting Fees/Honoraria	St Jude Medical, Steering Committee, RESPECT Trial
• Major Stock Shareholder/Equity	
• Royalty Income	
• Ownership/Founder	
• Intellectual Property Rights	
• Other Financial Benefit	

Background

- ~25% of all ischemic strokes are “cryptogenic”[1]
- 34-46% of ischemic strokes occur between 18-60 years[2,3]
- PFO present in 40-50% of cryptogenic stroke patients[4,5]
- Young and middle aged patients have continued exposure to PFO-related recurrence risk
- No RCT has reported long-term outcomes of PFO closure

[1] Hart et al. *Lancet Neurology* 2014;13:429-436.
[2] Putaala et al. *Stroke* 2009;40:1195-1203.
[3] Wolf et al. *Cerebrovascular Dis* 2015;40:129-135.
[4] Lechat et al. NEJM 1988;318:1148-1152.
[5] Webster et al. Lancet 1988;332:11-12.

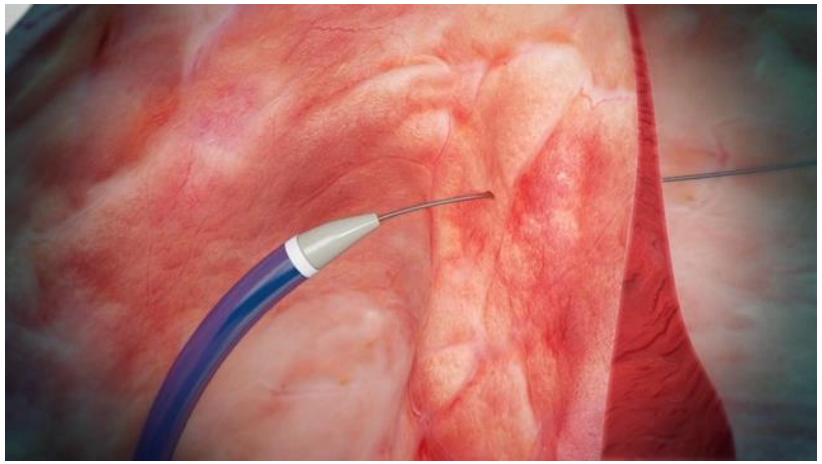
Background

- In the ITT population, early and medium-term results in in RESPECT showed point estimates in favor of closure but did not reach statistical significance
- RESPECT protocol required follow-up until an FDA regulatory decision
- Food and Drug Administration (FDA) Advisory Panel in May 2016 (data lock, August 2015)
- Following panel meeting, FDA requested an analysis of long-term outcomes using updated data – these final analyses (data lock, May 2016) of RESPECT are presented today
- Low event rates increase importance of longer follow-up

AMPLATZER™ PFO Occluder

Device Description:

- Self-expandable double disc device lined with thin polyester fabric
- Linked together by a short connecting waist
- Nitinol wire mesh
- Recapturable, repositionable
- Self-centering
- Distal and proximal radiopaque marker bands
- MR conditional
- End screw to facilitate optimal handling



Current status:

- CE-Mark in 1998; currently available in > 80 countries worldwide

RESPECT Trial

- Randomized, event-driven, open-label trial with blinded endpoint adjudication
- Patients randomized 1:1 to AMPLATZER™ PFO Occluder (device) vs. guideline-directed medical management (MM)
- 980 subjects enrolled from 2003 to 2011
- 69 sites in U.S. and Canada

Primary Endpoint

- **Composite of:**
  - Recurrent nonfatal ischemic stroke
  - Fatal ischemic stroke
  - Early post-randomization death (within 45 days)
- **Stroke definition:**
  - Acute focal neurological deficit due to cerebral ischemia with:
    - Neuroanatomically relevant infarct on imaging

      or

    - Symptoms >24 hours

Enrollment Criteria

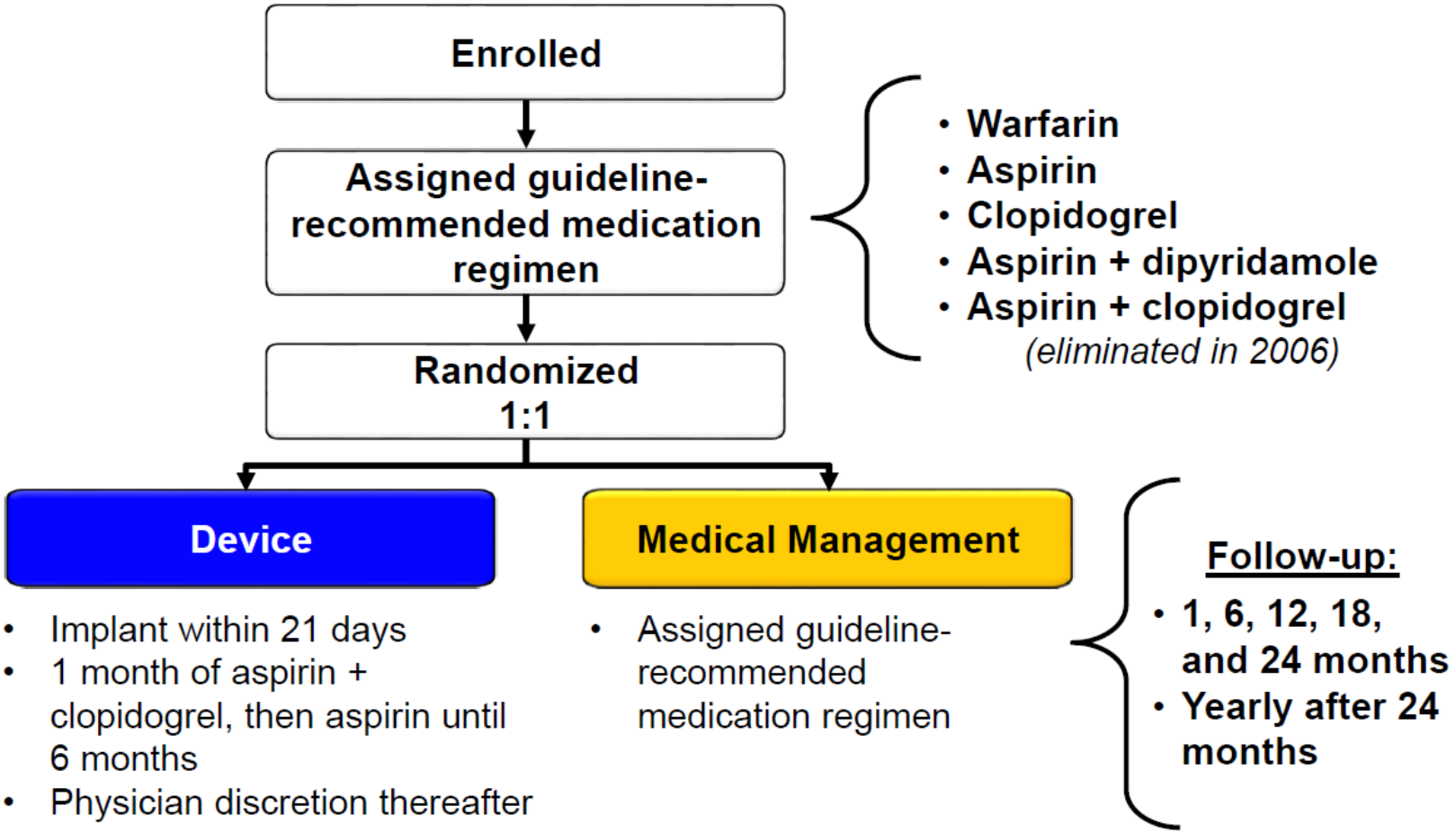
Key Inclusion Criteria

- **Cryptogenic stroke within last 9 months**
- **TEE-confirmed PFO**
- **18-60 years**
  - Patients > 60 at higher risk of recurrent stroke from non-PFO mechanisms

Key Exclusion Criteria

- **Stroke due to identified cause such as:**
  - Large vessel atherosclerosis (e.g., carotid stenosis)
  - Atrial fibrillation
  - Intrinsic small vessel disease (lacunar infarcts)
  - 11 other specific etiologies
- **Inability to discontinue anticoagulation**

Patient Flow



Objective of This Analysis

- To evaluate long term outcomes in RESPECT comparing the AMPLATZER™ PFO Occluder with guideline directed medical management

Methods

- Data from **August 2003 - May 2016**
- Intention-to-treat population
- Outcomes:
  - Recurrent ischemic strokes
  - Recurrent ischemic strokes of unknown mechanism
- Adjudications
  - **Adverse events** by the independent Data Safety Monitoring Board
  - **Ischemic stroke** by a blinded Clinical Events Committee
  - *Post hoc* adjudication of **cause** of recurrent ischemic stroke by a blinded committee of neurologists and a neuroradiologist (ASCOD phenotyping)

Baseline Characteristics Balanced Between Groups

Characteristic	AMPLATZER™ PFO Occluder (N=499)	Medical Management (N=481)
Age (yr), mean ± SD	48 ± 10	46 ± 10
Male	54%	56%
Hypercholesterolemia	39%	41%
Family h/o CAD	33%	33%
Hypertension	32%	32%
COPD	0.8%	1.5%
Congestive heart failure	0.6%	0%
History of DVT	4.0%	3.1%
Atrial septal aneurysm	36%	35%
Substantial shunt	50%	48%

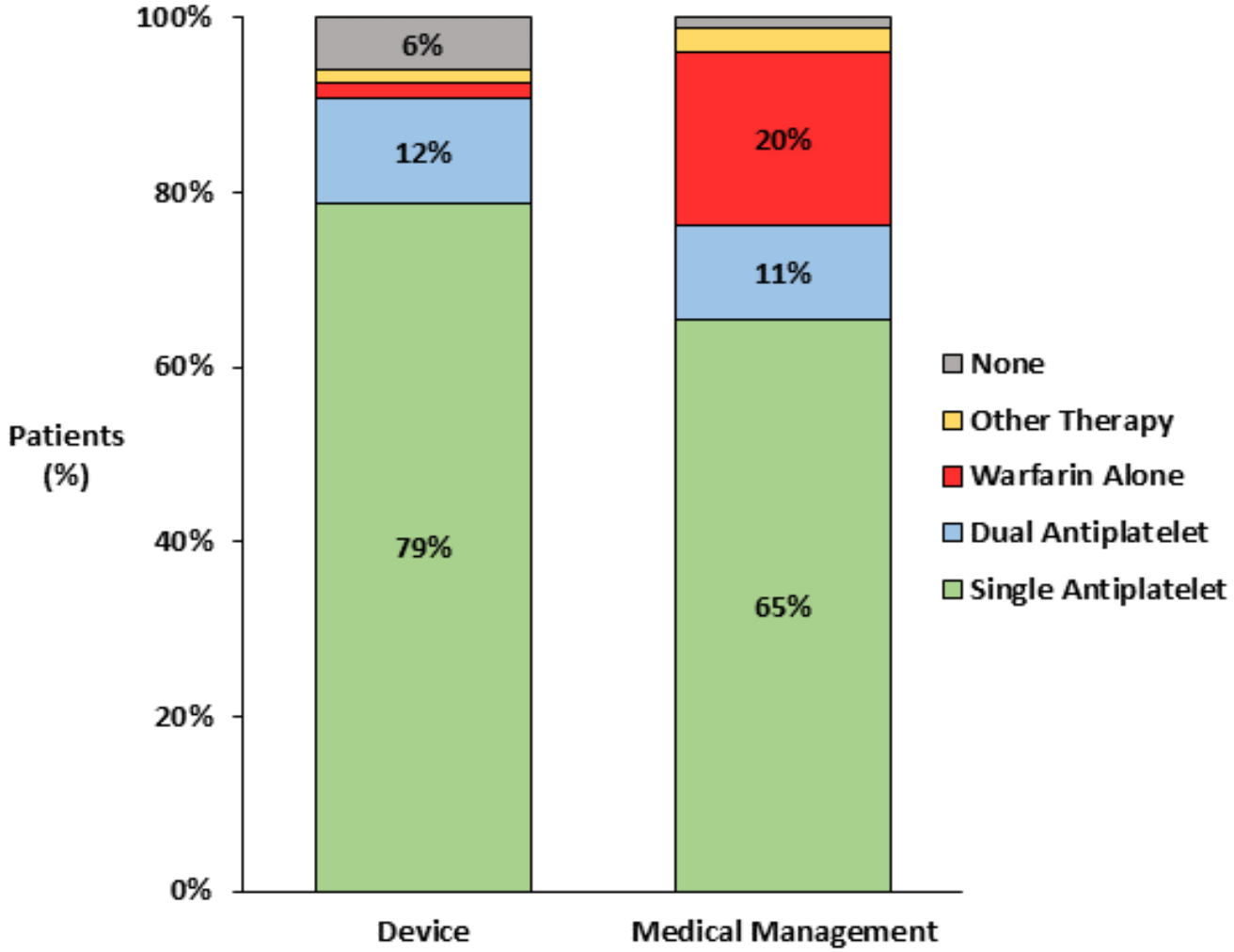
Procedural Results and Follow-up

- **Technical Success*** **99.1%**
- **Procedural Success**** **96.1%**
- **Mean Follow-up:** **5.9 years (0-12 years)**
  - Device
    - Mean 6.3 years; Total 3141 patient-years
  - Medical Management
    - Mean 5.5 years; Total 2669 patient-years

*Delivery and release of the device

**Implantation without in-hospital SAE

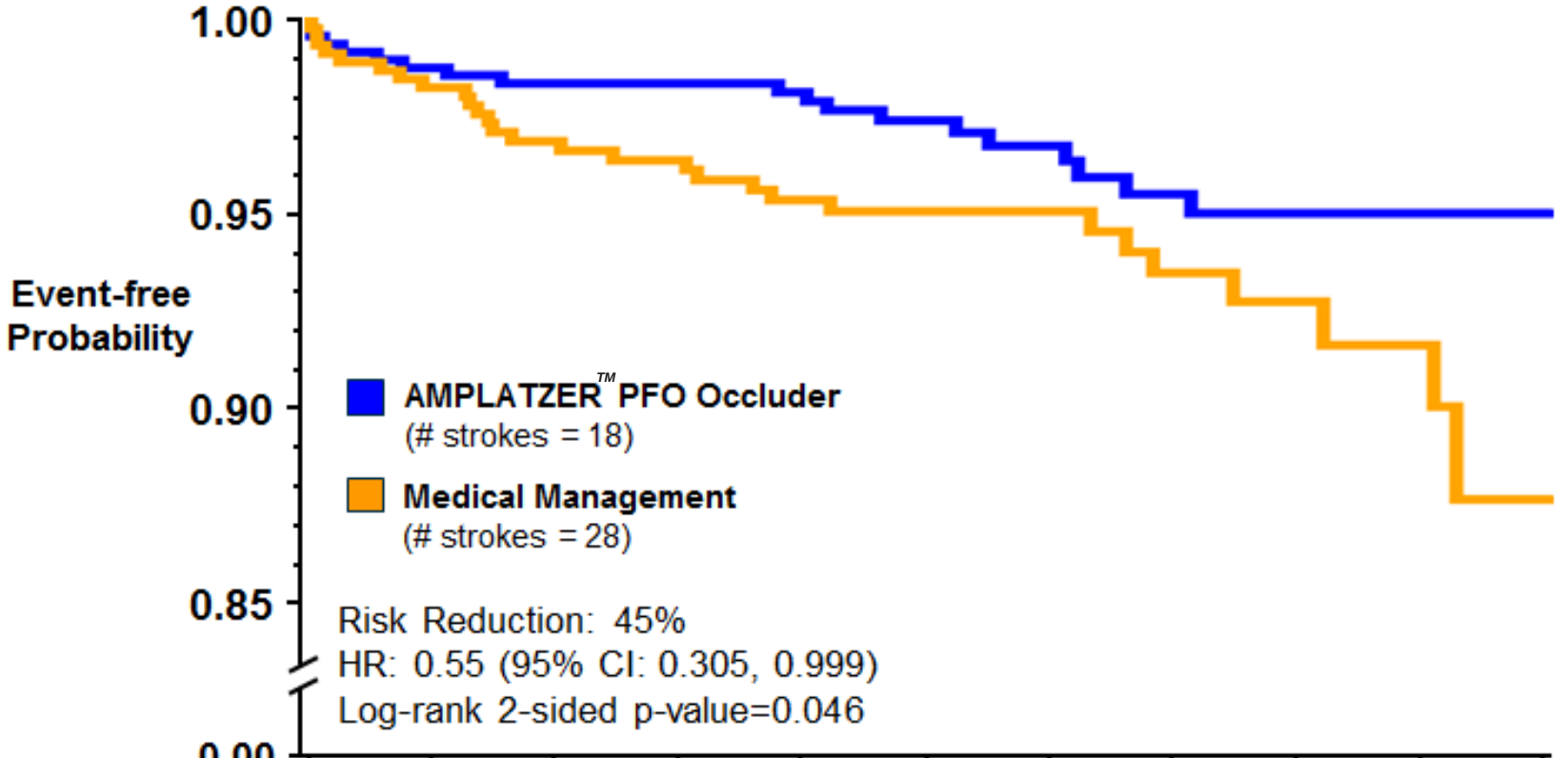
Antithrombotic Medication Use During Follow-up



RESULTS

RESPECT Final Results

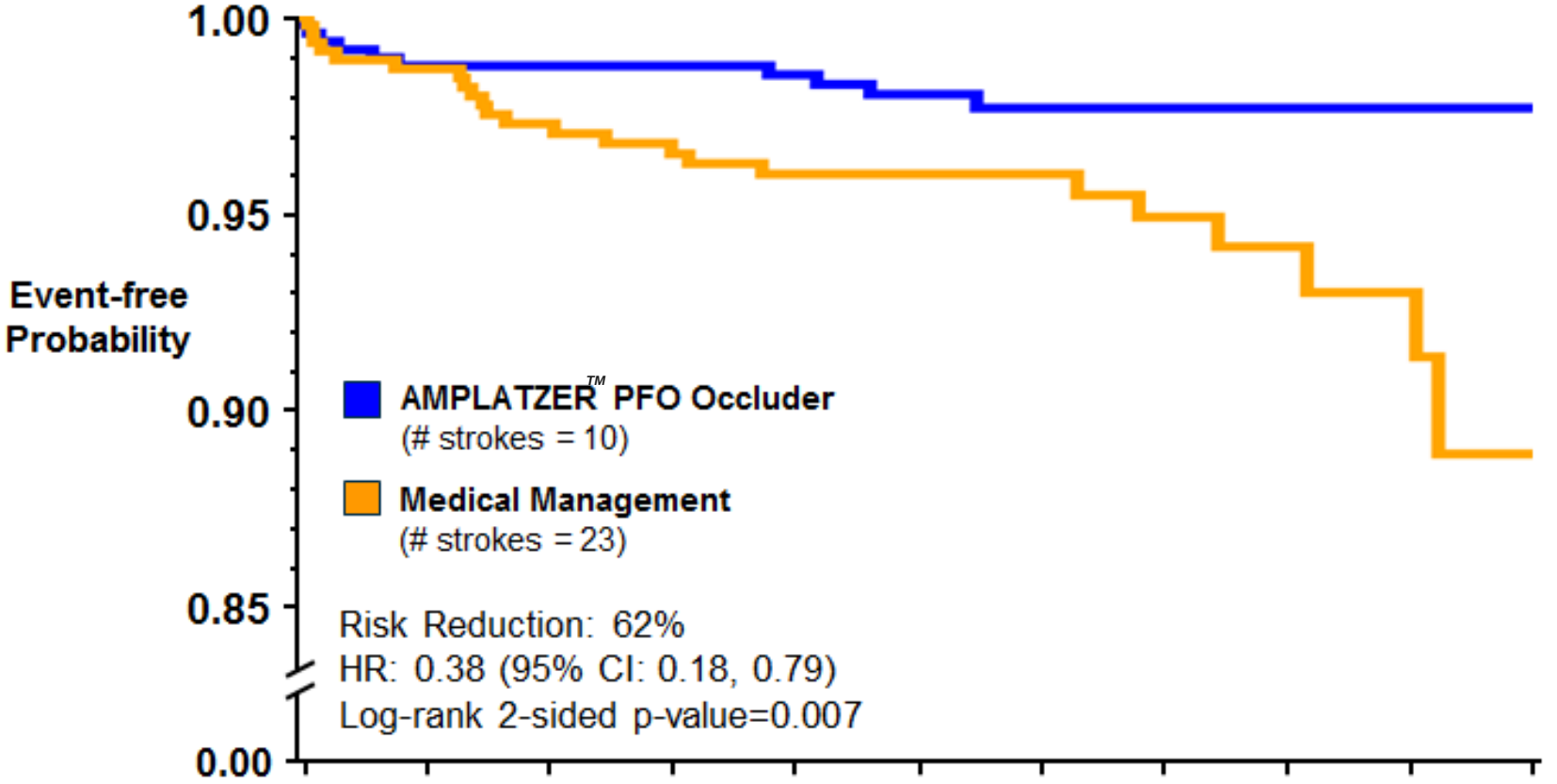
Freedom from Recurrent Ischemic Stroke (Intention to Treat)



# at Risk (KM Estimates)										
AMPLATZER	499 (0%)	476 (1.4%)	464 (1.6%)	447 (1.6%)	421 (1.9%)	352 (2.6%)	262 (3.3%)	197 (4.5%)	128 (5.0%)	77 (5.0%)	41 (5.0%)
MM	481 (0%)	433 (1.8%)	394 (3.2%)	380 (3.7%)	354 (4.7%)	282 (5.0%)	218 (5.0%)	150 (6.6%)	104 (7.3%)	59 (8.5%)	31 (12.5%)

RESPECT Final Results

Freedom from Recurrent Ischemic Stroke of Unknown Mechanism (Intention to Treat)



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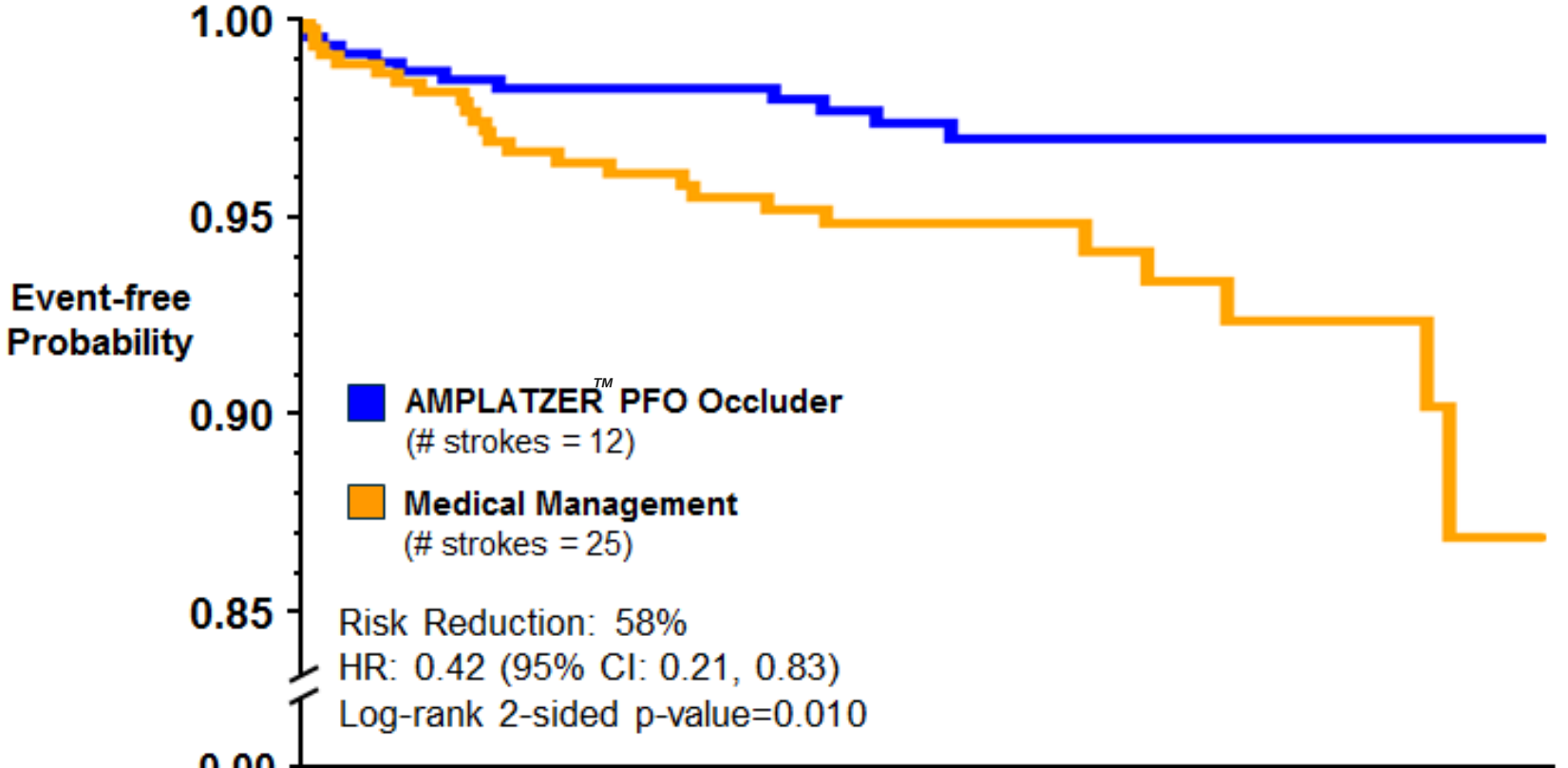
RESPECT Final Results

Freedom from Recurrent Ischemic Stroke (Intention to Treat – Patients censored at age 60 years)



# at Risk (KM Estimates)										
AMPLATZER	475 (0%)	443 (1.3%)	418 (1.8%)	383 (1.8%)	345 (2.0%)	285 (2.6%)	203 (3.0%)	150 (3.0%)	97 (3.0%)	55 (3.0%)	29 (3.0%)
MM	463 (0%)	402 (1.8%)	353 (3.4%)	321 (3.9%)	289 (4.9%)	220 (5.2%)	159 (5.2%)	109 (6.7%)	76 (7.7%)	44 (7.7%)	22 (13.2%)

Interpretation

- **These analyses support the hypothesis that PFO closure is preventing PFO-related recurrent strokes**
- **PFO-closure cannot prevent strokes from non-PFO related causes**

	HR (95% CI)	Relative Risk Reduction	P-value
Ischemic stroke	0.55 (0.305-0.999)	45%	0.046
Stroke without known mechanism	0.38 (0.18-0.79)	62%	0.007
Age-censored analysis (<60y)	0.42 (0.21-0.83)	58%	0.01

DSMB Adjudicated Procedure or Device Related SAEs

- No intra-procedural strokes
- No device embolization
- No device thrombosis
- No device erosion
- Major vascular complications (0.9%) and device explants (0.4%)

Adjudicated SAEs of Interest

Event Type	AMPLATZER™ PFO Occluder (N=499) [3141 Pt-Yrs]		Medical Management (N=481) [2669 Pt-Yrs]		P-value**
	Events	Rate*	Events	Rate*	
Atrial fibrillation	8	0.25	4	0.15	0.37
Major bleeding	18	0.57	15	0.56	0.96
Death from any cause	7	0.22	11	0.41	0.21
DVT/PE	18	0.57	4	0.15	0.006

* Rate expressed as number of events per 100 patient-years
**Based on the normal approximation to a difference in Poisson rates

Conclusions

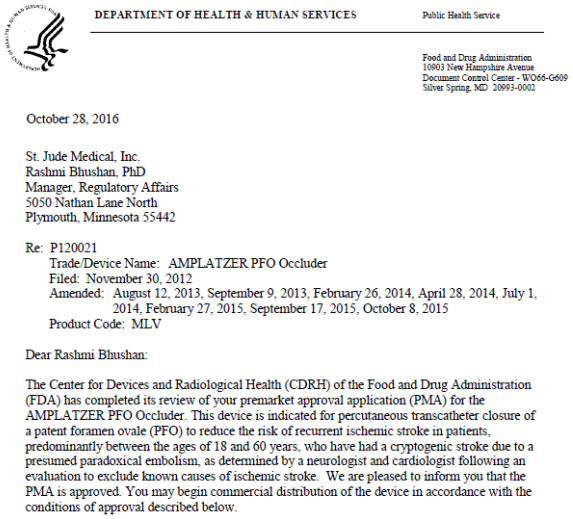
- **In the RESPECT trial, PFO closure with the AMPLATZER™ PFO Occluder was more beneficial than medical management alone**
- **Collaboration between a cardiologist and neurologist is important for proper patient selection**
- **For patients with cryptogenic stroke and PFO, closure with the AMPLATZER™ PFO Occluder is an appropriate treatment option that reduces the risk of recurrent stroke**

Thank You!

- To the incredible patients that volunteered to participate in this trial for their patience and willingness to help us answer an important question
- To the investigators and their tireless research teams for their professionalism and perseverance

FDA Approval 10/28/16

The AMPLATZER™ PFO Occluder is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.



DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

October 28, 2016

St. Jude Medical, Inc.
Rashmi Bhushan, PhD
Manager, Regulatory Affairs
5050 Nathan Lane North
Plymouth, Minnesota 55442

Re: P120021
Trade/Device Name: AMPLATZER PFO Occluder
Filed: November 30, 2012
Amended: August 12, 2013, September 9, 2013, February 26, 2014, April 28, 2014, July 1, 2014, February 27, 2015, September 17, 2015, October 8, 2015
Product Code: MLV

Dear Rashmi Bhushan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the AMPLATZER PFO Occluder. This device is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.