FDA Panel Questions (Draft)

St. Jude Medical's AMPLATZER™ PFO Occluder

Question 1: Evaluation of the RESPECT Primary Effectiveness Endpoint

The primary endpoint of the RESPECT trial was a composite of recurrent nonfatal stroke, post-randomization all-cause mortality, and fatal ischemic stroke. All primary endpoint events were recurrent nonfatal ischemic strokes. There were 9 primary endpoint events in the AMPLATZER PFO Occluder (the Device) group and 16 in the medical management (MM) group. Based on the pre-specified primary raw count analysis in the intention to treat (ITT) population, superiority of Device vs. MM was not achieved (p = 0.157). Throughout the trial, there was a differential drop-out rate (10.4% in the Device group vs. 19.1% in the MM group in the initial 20 May 2012 data lock). To account for differential follow-up, the statistical analysis plan was revised to supplement the raw count analysis with a Kaplan-Meier analysis and the log-rank test for the primary hypothesis. The Kaplan-Meier analysis showed a 50% risk reduction in the rate of recurrent non-fatal strokes that did not reach statistical significance (p=0.089), and the 95% CI is notably wide (0.221, 1.131). The raw count and Kaplan-Meier analyses are shown in **Table 1a**.

Table 1a. Primary endpoint outcomes in the ITT population

	Subjects N total (N_D/N_{MM})	Primary Endpoint Events N total (N_D/N_{MM})	Relative Risk (D vs MM) RR (95% CI)	Risk Reduction (1 - RR)	*P* value
ITT/Count	980 (499/481)	25 (9/16)	0.534 (0.234, 1.220)	46.6%	0.157
ITT/KM	980 (499/481)	25 (9/16)	0.500 (0.221, 1.131)	50.0%	0.089

Abbreviations: ITT, intent-to-treat; KM, Kaplan-Meier; D, Device; MM, Medical Management

An extended follow-up analysis was based on a data lock dated 14 Aug 2015. There were 18 primary endpoint events in the Device group and 24 in the MM group. The drop-out rate at the time of the extended follow-up data lock was 18.2% in the Device group vs. 30.1% in the MM group. The Kaplan-Meier analysis showed an event rate of 0.65 per 100 patient-years in the Device group and 1.01 per 100 patient-years in the MM group, hazard ratio 0.65, 95% CI: 0.35, 1.120, **Table 1b**).

Table 1b. Primary endpoint events (ITT analysis – extended follow-up)

	Subjects N total (N_D/N_{MM})	Primary Endpoint Events N total (N_D/N_{MM})	Relative Risk[a] (D vs MM) RR (95% CI)	Risk Reduction (1 - RR)	*P* value[b]
ITT/KM	980 (499/481)	42 (18/24)	0.65 (0.35, 1.20)	35.0%	0.16

[a] The relative risk is represented by the odds ratio.
[b] 2-sided p-value using the Fisher's Exact test.

Please comment on the clinical significance of these results.

Question 2: RESPECT Primary Endpoint Additional Analyses

In addition to the raw count and Kaplan-Meier analyses of event rates in the ITT population, the sponsor performed analyses on the Per Protocol, As Treated, and Device in Place populations using both the original PMA data lock (20 May 2012, **Table 2a**) and the extended follow-up data lock (14 Aug 2015, **Table 2b**).

Table 2a: Initial PMA data lock results

Cohort Analysis	Subjects N total (N_D/N_{MM})	Primary Endpoint Events N total (N_D/N_{MM})	Relative Risk (D vs MM)[a] RR (95% CI)	Risk Reduction (1 - RR)	*P* value[b]
PP/KM	937 (463/474)	20 (6/14)	0.371 (0.14, 0.97)	62.9%	0.034
AT/KM	950 (463/487)	21 (5/16)	0.280 (0.101, 0.77)	72.0%	0.008
DIP/KM	980 (464/516)	25 (6/19)	0.304 (0.122, 0.763)	69.6%	0.007

Abbreviations: PP, Per Protocol; AT, As Treated; DIP, Device in Place
[a] The relative risk is represented by the odds ratio.
[b] 2-sided p-value using the Fisher's Exact test.

Table 2b: Extended follow-up results

Cohort Analysis	Subjects N total (N_D/N_{MM})	Primary Endpoint Events N total (N_D/N_{MM})	Relative Risk (D vs MM)[a] RR (95% CI)	Risk Reduction (1 - RR)	*P* value[b]
PP/KM	937 (463/474)	37 (15/22)	0.58 (0.030, 1.12)	42.0%	0.10
AT/KM	950 (463/487)	38 (14/24)	0.51 (0.26, 0.99)	49.0%	0.04
DIP/KM	980 (464/516)	42 (15/27)	0.51 (0.28, 0.94)	49.0%	0.04

[a] The relative risk is represented by the odds ratio.
[b] 2-sided p-value using the Fisher's Exact test.

Statistical significance (unadjusted for multiplicity) was achieved in the analysis of the initial PMA data lock for the Per Protocol, As Treated, and Device in Place populations and in the analysis of the extended follow-up data lock for the As Treated and Device in Place populations. While these analyses suggest a potential Device benefit in reducing the rate of recurrent ischemic stroke, it should be noted that since the primary endpoint was not met, supplementary analyses are typically used to generate hypotheses for future studies. In addition, the following issues limit robustness of the results of the supplementary analyses:

- The analyses conducted on the extended follow-up data lock demonstrate a smaller difference in recurrent ischemic stroke rates in the Device vs. MM groups compared to the difference observed in the original PMA dataset.
- The rate of subject discontinuation was high in the RESPECT trial and numerically greater in the MM vs the Device group [30.1% vs. 18.2%., respectively, (extended follow-up data lock)].
- Atherosclerotic risk factors for stroke were common among enrolled subjects in both groups and 8.1% of subjects did not have imaging confirmation of their qualifying stroke, raising the possibility that the event that was considered the qualifying stroke in some subjects was not a cryptogenic and in which the pathophysiologic role of the PFO is uncertain.

Please comment on the clinical significance of these results.

Question 3: Safety Events

There was no pre-specified safety endpoint; safety events were presented descriptively. The proportion of Device group subjects with serious adverse events (SAEs) related to the Device or

implantation procedure was 4.5% (21 of 467 subjects with a Device implantation attempt). Selected SAEs limited to the Device or implantation procedure (Device group subjects only) are shown in **Table 3a**.

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

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 explantation	2	0.4%

Table 3b shows the rates of atrial fibrillation atrial flutter, and paroxysmal supraventricular tachycardia adjudicated as either SAEs or non-SAEs, stratified by treatment group.

Table 3b. Rates of atrial fibrillation

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	18	3.6%	20	0.72	9	1.9%	12	0.51
Paroxysmal Atrial Fibrillation	3	0.6%	3	0.11	0	0.0%	0	0.00
Atrial Flutter	2	0.4%	2	0.07	0	0.0%	0	0.00
PSVT[1]	5	1.0%	5	0.18	0	0.0%	0	0.00

[1]Paroxysmal supraventricular tachycardia

On a per-subject basis, the atrial fibrillation rate was 4.2% (21/499) in the Device group subjects 1.9% (9/481) in the MM group.

Table 3c shows the rates of deep venous thrombosis (DVT) and pulmonary embolism (PE) adjudicated as either SAEs or non-SAEs, stratified by treatment group.

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[1] or PE[2]	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

[1]Deep venous thrombosis. [2]Pulmonary embolism (all pulmonary embolism events were SAEs).

There were 18 patients (3.6%) in the Device group and 3 patients (0.6%) in the MM group who had a either a deep vein thrombosis or pulmonary embolism.

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

Complete PFO closure assessed by TEE and bubble study was a pre-specified secondary endpoint. **Table 4** shows the rates of complete PFO closure (shunt grade 0 at rest and grade 0 during Valsalva) and effective PFO closure (shunt grade 0 or 1 at rest and grade 0 or 1 with Valsalva) in subjects implanted with the Device and assessed by the Echo Core Lab.

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

PFO 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%)

Among 349 Device subjects with a Core Lab-assessed PFO shunt assessment at 6 months, 249 patients had a grade 0 shunt both at rest and with Valsalva, corresponding to a complete PFO closure rate of 71.3%. Therefore, residual shunting across the PFO was common, occurring in 28.7% of assessed subjects. It should be noted PFO closure assessment of the 6-month TEE by the Echo Core Lab was missing in approximately 25% of subjects implanted with the Device.

Please comment on whether Device implantation is associated with an acceptable rate of PFO closure.

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 presumed paradoxical embolism."

Please comment on this Indications for Use statement.

Question 6: Labeling

The sponsor provided draft labeling in the panel pack.

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

Question 7: Benefit-Risk Assessment

Stroke can be a devastating clinical event for the patients and families affected and has large public health implications. There are approximately 800,000 new or recurrent strokes per year in the US, of which 87% (or approximately 696,000) are ischemic strokes. It has been estimated that 25% of ischemic strokes (or approximately 174,000) are cryptogenic. PFO is a very common finding in the general population (present in approximately 25% of individuals). Therefore, it would be expected that many patients with cryptogenic ischemic stroke would be potential candidates for PFO closure.

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 of 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 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.

In considering benefit-risk, please comment on the following:

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: Proposed Post - Approval Study (PAS)

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.