### Title

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## TCT-30

### PREMIUM Trial: Double blind study of percutaneous closure of patent foramen ovale with the AMPLATZER® PFO Occluder as a treatment for migraine with or without aura

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**BACKGROUND** Population studies have identified a correlation between migraine and patent foramen ovale (PFO), and observational studies have reported that PFO closure results in improvement in migraine in some patients. The PREMIUM Trial was a randomized, sham-controlled, double blind study of percutaneous closure of PFO with the AMPLATZER® PFO Occluder (St. Jude Medical, Inc.) as a treatment for migraine with or without aura.

**METHODS** 230 subjects with medically intractable migraine with or without aura, who also had a patent foramen ovale (PFO), were randomized to either a sham procedure plus medical therapy (107) or percutaneous closure of the PFO plus medical therapy (123). Inclusion criteria for randomization included 6 - 14 days of migraine per month as assessed by a headache specialist, and failure (either lack of efficacy or intolerance) of 3 preventive medications and a significant right to left cardiac shunt (Spencer grade 4-5) determined by a screening TransCranial Doppler (TCD) intravenous agitated saline study. Subjects were randomized on the catheterization table after proof of a PFO was established, to device closure versus a sham control. Subjects and headache specialists were blinded to the randomization allocation. The primary efficacy endpoint was the responder rate percent defined as a 50% reduction in migraine attacks per month based on the diary during months 10-12 post randomization. Subjects in the control arm could receive the device after the 1-year blind was over. The primary safety endpoint was the proportion of subjects who experienced a device related serious adverse event through 1 year of follow-up.

**RESULTS** There was no difference in the responder rate between the device (38%) and the control groups (32%, p=0.3). The device was safe: there was 1/202 (0.5%) device related serious adverse event, which was a transient episode of atrial fibrillation. Secondary endpoint analysis showed a significant reduction in the total number of headache days (3.4 vs 2.0 days, p=0.03) in the device group. A subset analysis revealed that subjects for whom the majority of migraine attacks included aura had a particularly significant reduction in headache days (19/39, 49% responder rate vs 9/40, 23% responder rate, p=0.015). Complete remission of migraine occurred in 10.8% (8/74) of the device group and 1.5% (1/68) of controls who had a diagnosis of migraine with aura (p=0.02).

**CONCLUSIONS** Device closure of PFO can be performed safely, but did not result in a 50% or greater decrease in migraine attack frequency compared with a sham procedure, but there was a significant decrease in the mean number of headache days. Subgroup analysis suggests that individuals with aura occurring during the majority of their attacks may respond more favorably to PFO closure, and that a small but significant percentage of migraine with aura patients may experience complete remission of migraine.

**CATEGORIES STRUCTURAL:** Congenital and Other Structural Heart Disease

**KEYWORDS** Clinical Trial, Migraine, Patent foramen ovale