A Multicenter, Prospective, Single Arm, Open Label, Post-Market, Observational Study to evaluate the use of sTMS in reduction of Migraine Headache (ESPOUSE Study)

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Background

Single pulse transcranial magnetic stimulation (sTMS) has an FDA-approved acute treatment for migraine with aura. An open label study in the United Kingdom suggested a possible preventive benefit in migraine, and that study, plus the current trial, led to FDA approval of sTMS for migraine prevention in the US in July 2017.

Objective

The objective of this clinical trial was to evaluate the efficacy and tolerability of sTMS for the preventive treatment of migraine.

Methods

- The ESPOUSE Study was a multicenter, prospective, single-arm, open label, observational study to evaluate sTMS for the preventive treatment of migraine with or without aura.
- From December 2014 to March 2016, 263 patients with migraine were consented to complete a 1-month baseline headache diary followed by 3 months of treatment. The full analysis set (FAS) included patients who completed the baseline headache diary, met the inclusion criteria including 5-25 headache days per month, and used the device at least once.
- The treatment protocol consisted of both preventive (4 pulses twice daily) and acute treatment (3 pulses at 15 minute intervals repeated up to 3-times for each attack).
- The primary effectiveness endpoint (PEE), mean reduction of headache days compared to baseline, was measured over the 28-day period ending at 12 weeks. In the absence of a placebo control group, the PEE was compared to the performance goal, which is a statistically-derived, estimated placebo effect size, based on historical controls, of -0.6 day reduction of headache days from baseline.

Figure 1. Treatment Protocol

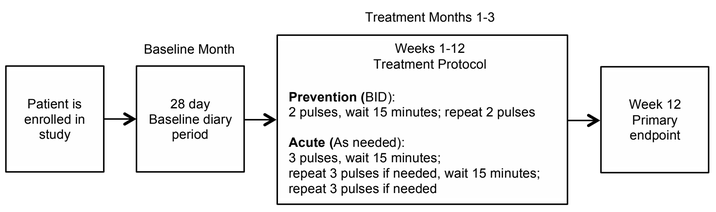
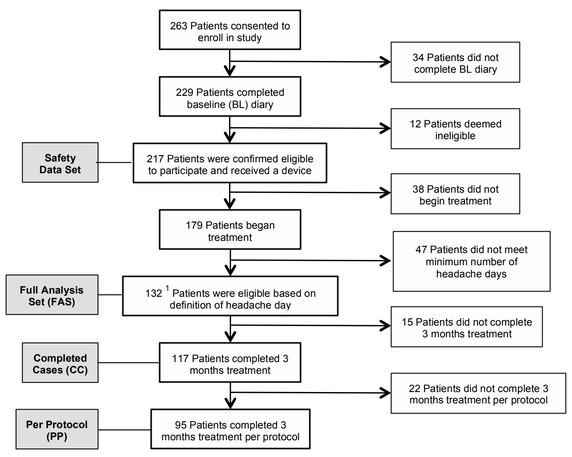


Figure 2. Subject Accountability Flow Chart



[1] Definition of Headache Day = 4 hours of pain at which point during the 4 hour period resulted in moderate to severe pain

Table 1. Baseline Quantitative Characteristics by Study Population

Characteristic	FAS Mean (SD) N[a] Med (Min, Max)	CC Mean (SD) N[a] Med (Min, Max)	PP Mean (SD) N[a] Med (Min, Max)
Age	42.82 (12.929) 130 43 (16, 65)	42.30 (13.160) 115 43 (16, 65)	42.98 (13.307) 93 43 (19, 65)
Height (in)	65.85 (3.700) 130 65 (59, 77)	65.82 (3.773) 115 65 (59, 77)	65.87 (3.972) 93 65 (59, 77)
Weight (lbs)	163.83 (44.659) 131 157 (63.64, 337.00)	162.86 (44.264) 116 155.66 (70.45, 337.00)	160.64 (42.266) 94 154.66 (70.45, 283.29)
Systolic Blood Pressure	121.69 (12.133) 131 122 (90, 160)	121.61 (15.175) 116 122 (90, 160)	122.21 (15.586) 95 123 (90, 157)
Diastolic Blood Pressure	77.12 (11.473) 131 78 (46, 101)	76.62 (11.678) 116 77 (46, 101)	77.08 (11.844) 95 78 (46, 101)
Age Migraine Began	19.59 (9.838) 132 17 (2, 51)	19.43 (9.790) 117 17 (2, 51)	19.56 (9.447) 95 17 (2, 51)

Table 2. Baseline Qualitative Characteristics by Study Population

Characteristic	FAS x/N (%)	CC x/N (%)	PP x/N (%)
Gender (Female)	106/132 (80.30)	94/117 (80.34)	76/95 (80.00)
Ethnicity			
Caucasian	113/132 (85.61)	103/117 (88.03)	85/95 (89.47)
African American	11/132 (8.33)	8/117 (6.84)	7/95 (7.37)
Hispanic	7/132 (5.30)	5/117 (4.27)	3/95 (3.16)
Other	1/132 (0.76)	1/117 (0.85)	0/95 (0.00)

Table 3. Reduction in Acute Medication Days in CC and PP Populations

Endpoint	Baseline Mean, (SD) N Med (Min, Max)	Change Mean, (SD) N Med (Min, Max)	95% Confidence Interval	t-statistic	P-value
Acute Medication Days (CC)	9.95 (5.63) 117 10.0 (0, 28)	-2.93 (5.24) 117 -2.0 (-23, 10)	(-3.89, -1.97)	-6.05	<0.0001
Acute Medication Days (PP)	10.38 (5.76) 95 10 (0, 29)	-3.18 (5.45) 95 -3 (-23, 9)	(-4.29, -2.07)	-5.69	<0.0001

Table 4. Reduction in HIT-6 score in CC and PP Populations

Endpoint	Baseline Mean, (SD) N Med (Min, Max)	Change Mean, (SD) N Med (Min, Max)	95% Confidence Interval	t-statistic	P-value
HIT6 (CC)	63.85 (4.56) 117 64.0 (50, 76)	-3.10 (6.42) 114[a] -2.0 (-25, 11)	(-4.29, -1.90)	-5.15	<0.0001
HIT6 (PP)	64.04 (4.56) 95 64 (52, 76)	-3.63 (6.79) 94[b] -2 (-25, 11)	(-5.02, -2.24)	-5.18	<0.0001

Table 5. Most Common Adverse Events Possibly or Probably Device-Related

Adverse Event	n	%
Light headedness	8/217	3.69%
Tingling	7/217	3.23%
Ringing in ears (tinnitus)	7/217	3.23%
Dizziness	6/217	2.77%
Headache	5/217	2.30%
Scalp discomfort	5/217	2.30%
Discomfort from noise	5/217	2.30%

Results

- A total of 263 subjects were consented, 229 completed a baseline diary, 220 subjects were found to be eligible based on the number of headache days, and 217 were assigned a device (safety data set). 132 subjects met the strict inclusion criteria based on the protocol definition of a headache day (4 or more hours of headache reaching moderate to severe pain), comprising the FAS. FAS baseline characteristics include: mean age of 42.8 years; 80.3% female; 85.6% Caucasian, 8.3% African American, 5.3% Hispanic, and 0.8% other.
- The PEE analysis was assessed in the FAS dataset. The mean reduction of headache days from baseline compared to the performance goal was statistically significant. There was -2.8 ± 0.4 mean reduction of headache days from baseline (9.1 days) in the FAS compared to the performance goal of -0.6 days (p<0.0001).
- 19.4% of subjects reported adverse events that were determined as “definitely”, “probably”, or “possibly” device-related. There were no serious adverse events. The top three adverse events were lightheadedness (4.5%), tingling (3.9%), and tinnitus (3.9%). 9 patients withdrew from the study because of adverse events.
- The PEE design allowed for a comparison to established placebo rates in migraine prevention, and the FDA accepted this design in approving sTMS in the preventive treatment of migraine.

Figure 3. Primary Effectiveness Endpoint: Mean Reduction in Headache Days

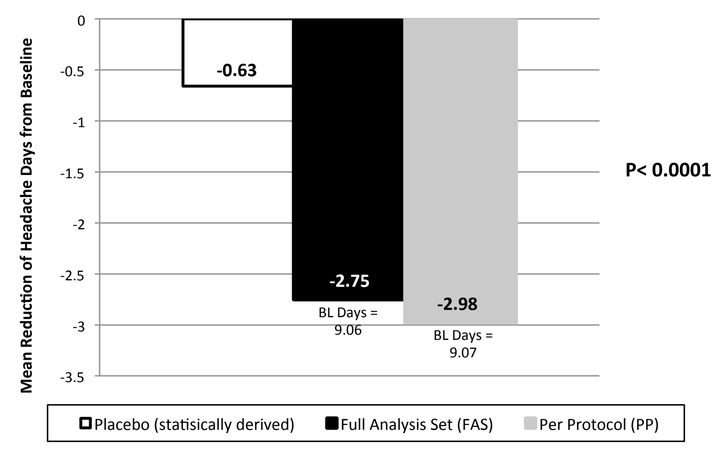
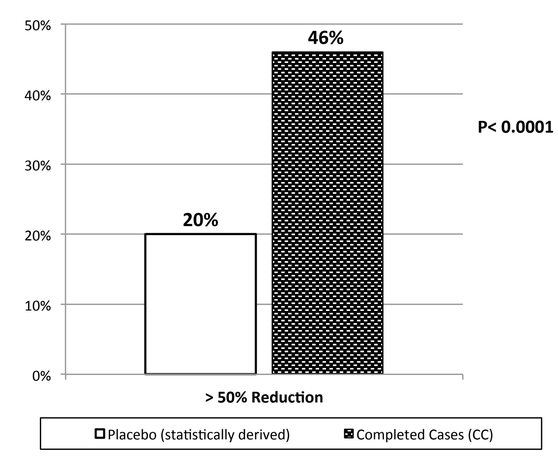


Figure 4. 50% Responder Rate



Conclusion

Based on the ESPOUSE study and a previous UK Study, the FDA has approved sTMS for the prevention of migraine.