Safety and Efficacy of Staged, Bilateral Focused Ultrasound Thalamotomy in Essential Tremor
An Open-Label Clinical Trial

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**IMPORTANCE** Unilateral magnetic resonance–guided focused ultrasound ablation of ventralis intermedius nucleus of the thalamus for essential tremor reduces tremor on 1 side, but untreated contralateral or midline symptoms remain limiting for some patients. Historically, bilateral lesioning produced unacceptable risks and was supplanted by deep brain stimulation; increasing acceptance of unilateral focused ultrasound lesioning has led to interest in a bilateral option.

**OBJECTIVE** To evaluate the safety and efficacy of staged, bilateral focused ultrasound thalamotomy.

**DESIGN, SETTING, AND PARTICIPANTS** This prospective, open-label, multicenter trial treated patients with essential tremor from July 2020 to October 2021, with a 12-month follow-up, at 7 US academic medical centers. Of 62 enrolled patients who had undergone unilateral focused ultrasound thalamotomy at least 9 months prior to enrollment, 11 were excluded and 51 were treated. Eligibility criteria included patient age (22 years and older), medication refractory, tremor severity (Clinical Rating Scale for Tremor [CRST] part A score ≥2 for postural or kinetic tremor), and functional disability (CRST part C score ≥2 in any category).

**INTERVENTION** A focused ultrasound system interfaced with magnetic resonance imaging allowed real-time alignment of thermography maps with anatomy. Subthreshold sonications allowed target interrogation for efficacy and off-target effects before creating an ablation.

**MAIN OUTCOMES AND MEASURES** Tremor/motor score (CRST parts A and B) at 3 months for the treated side after treatment was the primary outcome measure, and secondary assessments for efficacy and safety continued to 12 months.

**RESULTS** The mean (SD) population age was 73 (13.9) years, and 44 participants (86.3%) were male. The mean (SD) tremor/motor score improved from 17.4 (5.4; 95% CI, 15.9-18.9) to 6.4 (5.3; 95% CI, 4.9 to 7.9) at 3 months (66% improvement in CRST parts A and B scores; 95% CI, 59.8-72.2; P < .001). There was significant improvement in mean (SD) postural tremor (from 2.5 [0.8]; 95% CI, 2.3 to 2.7 to 0.6 [0.9]; 95% CI, 0.3 to 0.8; P < .001) and mean (SD) disability score (from 10.3 [4.7]; 95% CI, 9.0-11.6 to 2.2 [2.8]; 95% CI, 1.4-2.9; P < .001). Twelve participants developed mild (study-defined) ataxia, which persisted in 6 participants at 12 months. Adverse events (159 of 188 [85%] mild, 25 of 188 [13%] moderate, and 1 severe urinary tract infection) reported most commonly included numbness/tingling (n = 17 total; n = 8 at 12 months), dysarthria (n = 15 total; n = 7 at 12 months), ataxia (n = 12 total; n = 6 at 12 months), unsteadiness/imbalance (n = 10 total; n = 0 at 12 months), and taste disturbance (n = 7 total; n = 3 at 12 months). Speech difficulty, including phonation, articulation, and dysphagia, were generally mild (rated as not clinically significant, no participants with worsening in all 3 measures) and transient.

**CONCLUSIONS AND RELEVANCE** Staged, bilateral focused ultrasound thalamotomy significantly reduced tremor severity and functional disability scores. Adverse events for speech, swallowing, and ataxia were mostly mild and transient.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier NCT04112381.

JAMA Neurol. doi:10.1001/jamaneurol.2024.2295
Published online July 29, 2024.
essential tremor (ET) is one of the most common movement disorders. Surgery targeting the ventralis intermedius nucleus of the thalamus is an effective treatment for ET in patients with functionally significant tremors. Deep brain stimulation has been the established procedure for refractory ET as it can be adjusted to maximize efficacy and reduce off-target adverse effects.

Alternatively, magnetic resonance–guided focused ultrasound (MRgFUS) thalamotomy uses intersecting ultrasound beams to ablate the ventralis intermedius to reduce contralateral tremors. A randomized, controlled, blinded trial of unilateral MRgFUS thalamotomy for ET showed sufficient efficacy and safety that the procedure was approved by the US Food and Drug Administration (FDA) in 2016.

All the initial MRgFUS studies, as well as the first FDA approval, were for unilateral treatment for the dominant hand. However, most patients with ET have bilateral symptoms, and often require bilateral surgery. Also, for clinically significant head and voice tremors, unilateral surgery is usually inadequate to provide satisfactory control. Recently, a few small, single-center studies of staged bilateral MRgFUS thalamotomy for ET, have shown initial efficacy and safety similar to unilateral treatment.

The growing acceptance of unilateral MRgFUS ablation has led to an interest in a bilateral option, but historically bilateral ablation was associated with higher risks, such as speech and language disturbance. Therefore, we designed a sufficiently robust study to allow regulatory evaluation of the safety and effectiveness of staged, bilateral MRgFUS thalamotomy. We now report the results of a multicenter trial of contralateral MRgFUS thalamotomy in individuals with ET with a previously successful unilateral MRgFUS thalamotomy. These results were used by the FDA to approve staged bilateral MRgFUS ablation for ET.

Methods

Trial Design and Oversight
The trial was performed under investigational device exemption and registered with ClinicalTrials.gov. Seven sites in the US recruited and treated participants between July 2020 and October 2021. Clinical oversight for each site was provided by the principal investigator and an independent centralized data and safety monitoring board. The sponsor and device manufacturer, Insightec, provided trial oversight for regulatory processes. The study investigators participated in statistical analysis in collaboration with an independent data analysis company (Technostat) contracted by the sponsor. The study protocol (Supplement 1) was approved by the institutional review boards at each institution, and written informed consent was signed by all participants. There were no confidentiality agreements between the sponsor and trial investigators. The trial was conducted in accordance with the Helsinki/Harmonization guidelines. Some features of the study design, including specific outcome scales, were chosen to conform with the preferences of regulatory bodies.

The study was a prospective, open-label, uncontrolled, single-arm, cohort, multicenter trial designed to evaluate the safety and effectiveness of staged, bilateral MRgFUS thalamotomy in individuals with medication-refractory ET. Individuals screened for eligibility had already undergone unilateral MRgFUS thalamotomy, 5 of whom participated in the earlier randomized study. MRgFUS thalamotomy for the untreated side was performed at least 9 months following initial treatment. Since participants had undergone a prior MRgFUS thalamotomy, it would make blinding of participants difficult, as they were fully aware of treatment-associated sensations and that expected improvement was virtually immediate.

Study Population
Sample size was based on the original unilateral study, accounting for a potential dropout rate of 20%. All participants consented and were screened, and those not meeting the following eligibility criteria were excluded: aged 22 years or older, diagnosis of ET that is refractory to adequate trials of at least 2 medications (at least 1 first line), history of previous MRgFUS thalamotomy procedure at least 9 months prior to enrollment, baseline Clinical Rating Scale for Tremor (CRST) part A score of 2 or higher for postural or kinetic tremor severity in the upper extremity for the untreated side, baseline CRST part C score of 2 or higher in any category. Exclusion criteria included persistence of any neurological worsening following the index procedure, a physical subscale score of 16.5 or greater on the Dysphagia Handicap Index or a diagnosis of dysphagia, clinically significant abnormal speech function, a score of less than 22 on the Montreal Cognitive Assessment, pregnant or breastfeeding, unstable cardiac status disease, prior deep brain stimulation or stereotactic ablation, coagulopathy, a skull density ratio (indicating the degree of penetrability of acoustic energy) less than 0.40, a structural brain lesion or a history of intracranial hemorrhage, multiple strokes, or a stroke within the past 6 months. Anticoagulation medications were stopped prior to and immediately after the MRgFUS procedure. Race and ethnicity data were gathered due to known differences in skull density ratio, but data are not reported here owing to small numbers.

Procedure
MRgFUS thalamotomy was performed using Exablate 4000 Neuro (Insightec) interfaced with a magnetic resonance...
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Follow-Up Assessments
Follow-up assessments were performed at 48 hours and months 1, 3, 6, and 12. Assessments included physical and neurological examinations (including walking and ataxia), CRST score, Dysphagia Handicap Index score, speech function assessments, Montreal Cognitive Assessment score, Epworth Sleepiness Scale (ESS) score, medication review, and adverse events.

Outcome Measures
All adverse events occurring during the study were recorded and assessed for causality and severity (mild, moderate, and severe; defined in the protocol according to FDA definitions). The primary study end point for safety was the incidence and severity of device- and treatment-related adverse events occurring through the 6-month time point and followed until the end of the study at 12 months.

Statistical Analysis
Data were analyzed using SAS version 9.4 (SAS Institute). Numerical variables were tabulated using means, SDs, and 95% CIs. Categorical variables were summarized using the number of observations and percentages. The study had 1 primary and 2 secondary efficacy end points. A hierarchical testing design was used to control for multiplicity across the end points. The primary efficacy analysis was performed with a significance level of \( \alpha = .05 \). Testing of the 2 secondary efficacy end points proceeded with \( \alpha = .05 \) if all previous tests were successful. Primary efficacy analyses were conducted on the modified intent-to-treat analysis set, which included all participants with baseline and at least 1 posttreatment measurement on the primary efficacy data. Primary and secondary end points were prespecified and approved by the FDA prior to initiation of the study. Data are reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Results

Study Population
Sixty-two individuals with a previous MRgFUS thalamotomy were recruited. Eleven were excluded (3 in whom CRST scores did not meet inclusion criteria, 3 with presence of dysphagia or elevated Dysphagia Handicap Index score, 1 with a low skull density ratio, 1 with clinically significant dysarthria, 1 with contraindicated medication use, 1 with a persistent neurological event, and 1 who withdrew consent during screening). There-
Tremor Outcomes

At 3 months posttreatment, the primary outcome measured by CRST parts A and B reduced from a mean (SD) score of 17.4 (5.4; 95% CI, 15.9 to 18.9) to 6.4 (5.3; 95% CI, 4.9-7.9; 66% reduction in the CRST parts A and B; 95% CI, 59.8-72.2; P < .001) (Figure 2A). Mean (SD) postural tremor improved from 2.5 (0.8; 95% CI, 2.3-2.7) to 0.6 (0.9; 95% CI, 0.3-0.8; 81% reduction in the CRST part A; P < .001) (Figure 2B). These decreases in scores were similar at 6 and 12 months posttreatment (Figure 2), with CRST A and B mean (SD) tremor scores of 6.9 (5.0; 63% reduction) at 6 months and 7.0 (5.6; 62% reduction) at 12 months. Mean (SD) postural tremor scores also improved at 6 (0.5 [0.7];

81.2% reduction in CRST part A) and 12 (0.6 [0.8]; 80.2% reduction in CRST part A) months (P < .001 for all).

For the CRST part C, which reflects functional disability, the mean (SD) scores improved from 10.3 (4.7; 95% CI, 9.0-11.6) prior to the second side treatment to 2.2 (2.8; 95% CI, 1.4-2.9; 73% improvement in CRST part C; P < .001) (Figure 2C). Again, this was consistent across all the time points (mean [SD] 6-month score: 2.3 [3.9]; improvement of 73.1%; 12-month score: 2.4 [3.8]; 73.3% improvement in CRST part C; P < .001 for all) (Figure 2). Those participants who were taking primidone or propranolol at the time of screening for this study (n = 6) all reduced their doses by 6 months following the treatment (eFigure in Supplement 2). In 3 of these 6 patients, tremor medications were discontinued entirely by 3 months posttreatment.

Participant-Reported Adverse Events

Adverse events were 85% mild (159 of 188), 13% moderate (25 of 188), and 2% severe (1 severe urinary tract infection related to catheter use during procedure). The most common participant-reported adverse events within 30 days were numbness or tingling (mild, n = 17), dysarthria (mild, n = 14; moderate, n = 1), ataxia (mild, n = 12), unsteadiness/imbalance (mild, n = 9; moderate, n = 1), dysgeusia (mild, n = 6; moderate, n = 1), gait disturbance (mild, n = 5), and dysphagia (mild, n = 3; moderate, n = 1) (Table 2). At 3 months, 9 participants continued to experience numbness (all mild), 8...
reported dysarthria (all mild), 8 reported ataxia (all mild), 3 reported unsteadiness/imbalance (mild, n = 2; moderate, n = 1), 7 reported dysgeusia (mild, n = 6; moderate, n = 1), 3 reported dysphagia (mild, n = 2; moderate, n = 1), and 2 reported gait disturbance (all mild). At 12 months, 8 participants continued to experience numbness (all mild), 7 reported dysarthria (all mild), 6 reported ataxia (all mild), none reported unsteadiness/imbalance, 3 reported change in taste (mild, n = 2; moderate, n = 1), and 1 reported gait disturbance (mild). One severe event, a urinary tract infection due to catheter use during the treatment, was noted.

Speech and Language Pathology Assessment

The assessment by the speech and language pathologist identified that phonation shifted from baseline nonsignificantly abnormal to significantly abnormal in 1 participant at 1 month and 3 participants at 6 months. No other participants developed new difficulties with phonation.

At 1 month posttreatment, articulation in 1 participant changed from nonsignificant to significant, and 4 additional participants developed significant slurred/slow speech. By 3 months, 3 participants had ongoing, abnormal, significant articulation difficulty.

Table 2. Adverse Events Associated With Staged, Bilateral Focused Ultrasound Ablation

<table>
<thead>
<tr>
<th>Event</th>
<th>No.</th>
<th>Total (N = 51)</th>
<th>1 mo (n = 51)</th>
<th>3 mo (n = 50)</th>
<th>6 mo (n = 50)</th>
<th>12 mo (n = 47)</th>
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<tbody>
<tr>
<td>Numbness/tingling</td>
<td>17</td>
<td>11</td>
<td>9</td>
<td>8</td>
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<tr>
<td>Dysarthria</td>
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<td>10</td>
<td>8</td>
<td>7</td>
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<tr>
<td>Ataxia</td>
<td>12</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>6</td>
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<tr>
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<td>Dysgeusia</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Gait disturbance</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>1</td>
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<td>Hypoguesia</td>
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<tr>
<td>Dysphagia</td>
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<td>3</td>
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<tr>
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<tr>
<td>Facial droop</td>
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<td>0</td>
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</tr>
<tr>
<td>Weakness</td>
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<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Decrease in synchronicity</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
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<tr>
<td>Diplopia, intermittent</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Dizziness</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Dry mouth</td>
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<td>1</td>
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<tr>
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<tr>
<td>Sialorrhea</td>
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<td>1</td>
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<tr>
<td>Voice change</td>
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</tr>
</tbody>
</table>

a All events were mild, except for 1 moderate event each for dysarthria (resolved by 1 month), unsteadiness/imbalance (resolved by 6 months), dysgeusia (ongoing at 12 months), dysphagia (ongoing at 12 months), and headache (resolved by 1 month).
b Mild difficulty in coordinating the right and left hand when playing the guitar.
c There was 1 severe event, a urinary tract infection due to catheter use during the treatment.
Nine participants were observed to have significant abnormal dysphagia at 1 month (2 at baseline and 7 additional participants developed abnormal dysphagia). By 6 months, the number of dysphagia abnormalities reduced to 3 participants with significant abnormal dysphagia and 1 with nonsignificant abnormal dysphagia. No participant had worsening in all 3 speech and language measures.

Additional Safety Assessments
Among other clinical evaluations, there were no significant changes in cognition as measured by the Montreal Cognitive Assessment (mean [SD] at baseline, 26.5 [1.9], 6 months, 27.3 [2.6]), and Epworth Sleepiness Scale results remained unchanged (participants with reported normal sleep at baseline, n = 46; 3 months, n = 43; and 6 months, n = 46).

Secondary Outcomes
Among participants with baseline voice tremor, 8 of 12 (67%) were considered treatment responsive, and there was a mean (SD) improvement from 1.2 (0.5) at baseline to 0.2 (0.4) at 3 months, 0.4 (0.5) at 6 months, and 0.3 (0.5) at 12 months (Figure 3). For participants with head tremor prior to contralateral treatment, 12 of 17 (71%) were responders, with a mean (SD) improvement from the head tremor score at baseline of 1.1 (0.3) to 0.4 (0.6) at 3 months, 0.4 (0.6) at 6 months, and 0.2 (0.4) at 12 months.

Discussion
In this multicenter, open-label trial of 51 participants with ET, staged bilateral MRgFUS thalamotomy significantly reduced limb, head, and voice tremor and improved tremor-related disability. These improvements were associated with adverse events similar in frequency and severity to those that occurred in the pivotal trial of unilateral treatment,4 with the exception of mild dysarthrias, which were reported more frequently in this study. These data led to regulatory approval by the US FDA, yet this is the first report of these data from the study.

Unilateral MRgFUS thalamotomy is increasingly used for patients with tremor refractory to medical therapy due to its less invasive nature and elimination of hardware implants. However, a PubMed search revealed 87 publications reporting MRgFUS thalamotomy outcomes, and most were unilateral procedures. Most patients with ET have bilateral symptoms, and the untreated limb can be a continuing source of disabling symptoms after successful unilateral treatment for the many daily tasks requiring the use of both hands, as indicated by the ongoing baseline mean disability score in this study prior to contralateral treatment.

This is the first study that we are aware to include a pre- and post-MRgFUS thalamotomy formal speech and language assessment. After MRgFUS thalamotomy, we observed adverse events related to speech and swallowing function, which were much less frequent than the reported rates of speech dysfunction after bilateral radiofrequency thalamotomy.10 However, there were no clear patterns to predict which participants might be more prone to a decline. While the frequency of these adverse events was greater than prior reports of unilateral treatment, most were sufficiently mild that they were not considered to be a source of clinical disability for participants. Adverse events in these domains have also been reported in studies of bilateral deep brain stimulation for ET.17,18

At 1 month following the procedure, approximately 20% of participants reported sensory changes (numbness or tingling), dysarthria, or ataxia, and a loss or change in taste (dysgeusia/hypogeusia). More than 60% of these resolved by 12 months. Nonetheless, at 12 months, 10% to 15% of participants reported some residual sensory changes, dysarthria, or gait ataxia, all of which were reported as mild and were thus defined as changes that did not interfere with everyday activities. Moderate dysphagia and dysgeusia were observed at 12 months in 1 participant each. The 1 severe event was a urinary tract infection due to catheter use during the treatment.
Differences in these adverse effects compared with prior studies may be due to intrinsic differences in cohorts or treatment.19 The magnitude and stability of tremor relief over 1 year is similar to the reported results from unilateral MRgFUS and the few studies of staged, bilateral MRgFUS thalamotomy.7–9 For those with head or voice tremors, there was a considerable reduction in tremor in most participants. These results are consistent with observations that bilateral deep brain stimulation treatment often better controls head and voice tremor.20 Participants were motivated to undergo contralateral treatment, suggesting that the ongoing contralateral tremor was sufficiently influencing their quality of life to justify undergoing a second procedure with limited safety and efficacy data prior to enrollment in this study. Thus, the significant improvement in functional scores following successful contralateral treatment confirms that even with an excellent result from unilateral therapy, staged bilateral treatment should be considered in patients with ongoing disability from contralateral tremor.

Limitations
A sham control group was considered, as was done in the unilateral ET trial4 and the unilateral pallidotomy trial (n = 94).21 In the pallidotomy trial, patients were assigned to 2 groups, treatment and sham. Although none of these participants had ever been treated with MRgFUS, 95% correctly believed that they had received active treatment, while in the sham group, 58% believed incorrectly that they were treated. But perhaps more relevant, the trial investigators correctly guessed 79% in the active group and 83% in the sham group. Given this experience, and considering this study population had already undergone unilateral treatment, we proceeded with an open-label study, recognizing this limitation. The nature of the study population, with improvement following unilateral MRgFUS thalamotomy and being mostly non-Hispanic White and mostly male, is another limitation. The skull density ratio has been noted to be lower on average in certain racial groups,22 which could have skewed the treatment population. The lack of other underrepresented groups may also reflect disparities in health care access.

Conclusions
In this open-label study of 51 participants, staged, bilateral MRgFUS thalamotomy significantly reduced tremor severity and functional disability scores. Adverse events for speech, swallowing, and ataxia were mostly mild and transient.
Research

Original Investigation

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E8 JAMA Neurology Published online July 29, 2024