Non-Invasive, At-Home Use Neuromodulation Device Provides Symptomatic Relief from Essential Tremor: Results From The PROSPECT* Study

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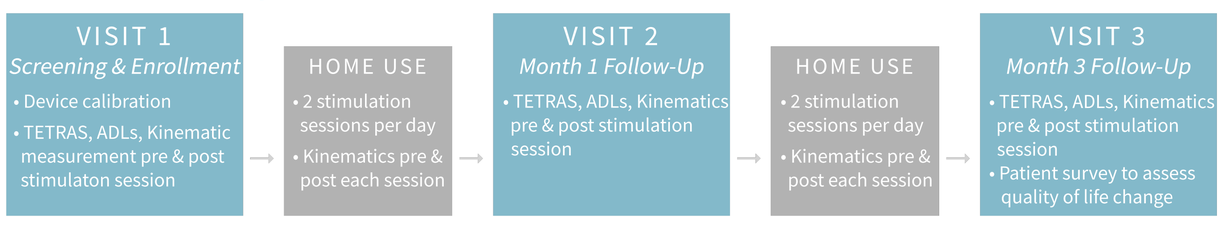
Objective & Study Timeline

This study evaluated the safety and efficacy of daily use of a wrist-worn neuromodulation device delivering non-invasive transcutaneous afferent patterned stimulation (TAPS) therapy for symptomatic relief from hand tremors in adults with essential tremor (ET) over a three month at-home trial, with sparse in-clinic visits.

Study Timeline: In-Clinic Visits and Home Use of Device

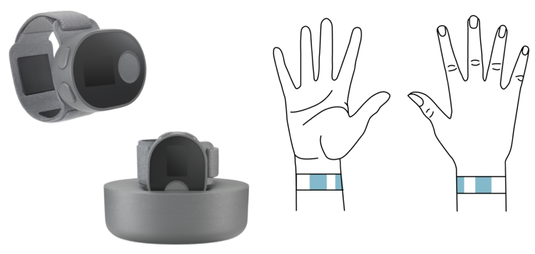


The study consisted of three in-clinic visits over three months with interim daily home-use of the neuromodulation therapy. Patients were screened for study eligibility, gave informed consent, and were fitted with the device at the first visit. Primary clinical endpoints were assessed at each of the three in-clinic visits, and secondary kinematic endpoints were assessed throughout the home-use sessions.

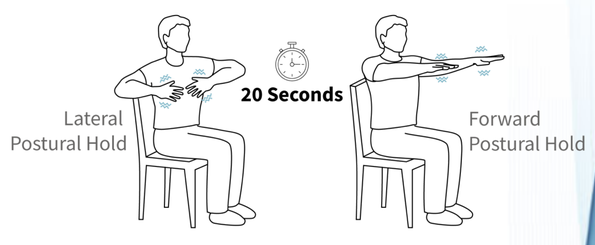
Methods: Patient Enrollment and Study Timeline. We conducted a prospective, multi-center, single-arm, three month study with 263 ET patients enrolled across 26 sites. Patients were seen for three in-clinic visits for screening and to establish tremor baseline (Visit 1), and for one-month (Visit 2) and three-month (Visit 3) follow-ups. Following study inclusion screening, patients were fitted with the TAPS device on the dominant hand. The neuromodulation stimulation frequency was calibrated to each patient's tremor frequency, and stimulation amplitude was increased to each patient's comfort level. Following in-clinic calibration and evaluation of device efficacy, patients were instructed to use the device on their dominant hand at home twice-daily for 40-minute stimulation sessions. 205 patients completed their third in-clinic visit and were included in the primary clinical endpoint analyses. 193 of the 205 patients had valid at-home session data, and were included in the secondary kinematic endpoint analyses.

Design & Methods

Device, Base Station & Electrode Placement



Device Calibration Postures



Device Design and Patient-Specific Calibration for Stimulation

*The device consisted of a **stimulator** and **detachable band** containing two working electrodes positioned over the median and radial nerves, and a counter-electrode positioned on the dorsal surface of the wrist.*

***Patient tremor frequency** was captured during a 20 second postural hold (middle 12 seconds recorded by the device). The peak tremor frequency was determined onboard the device and used to determine a patient-specific stimulation pattern.*

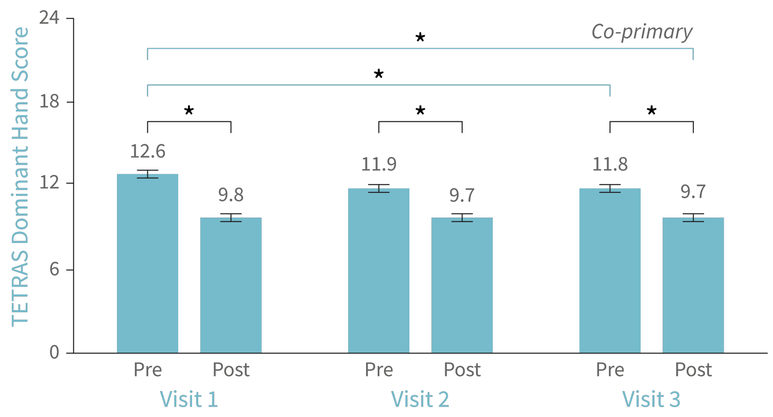
Methods: Assessed Clinical and Kinematic Endpoints. Pre-specified co-primary clinical endpoints evaluated at the in-clinic visits included hand-tremor specific tasks from the Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS) and Bain & Findley Activities of Daily Living (ADL) Scale, rated on the dominant hand. Additionally, the device's onboard accelerometers were used to measure per-session tremor power during a postural hold before and immediately after stimulation for each at-home stimulation session. Per-patient median pre-stimulation, post-stimulation, and fold-improvement in tremor power were computed over all stimulation sessions. At the study's conclusion, clinicians and patients were asked to rate the tremor improvement, and patients were surveyed on ease of use of the device, duration of benefit from a stimulation therapy session, and quality of life improvement.

In-Clinic Physician-Rated TETRAS and Patient-Rated ADL Score Improvements

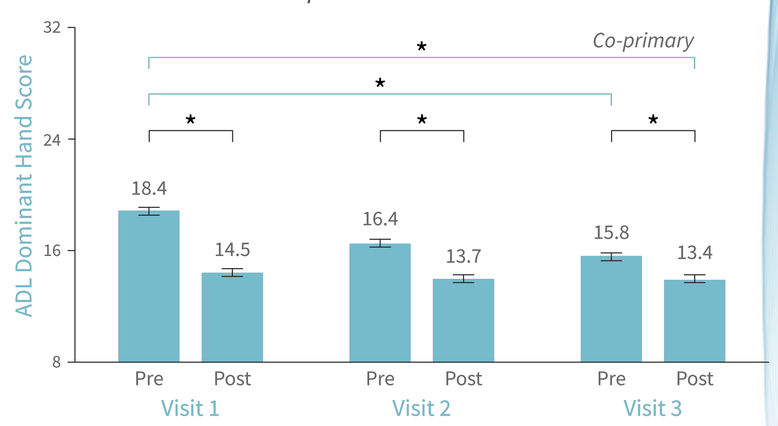
Primary Clinical Endpoint Improvements: Pre- and Post-Stimulation Per In-Clinic Visit

***Physician-rated TETRAS dominant hand score (left) and patient-rated ADL dominant hand score (right) significantly improved** before and after the therapy session conducted at each visit (n = 205, p < 0.0001). Clinician and patient-rated pre-stimulation tremor improved significantly over three months of use (p < 0.0001). Post-stimulation tremor rating after three months of therapy was significantly better than baseline pre-stimulation tremor rating (p < 0.0001). In all plots, error bars represent one standard error of the mean, and (*) indicates p < 0.0001.*

TETRAS Improvement Per In-Clinic Visit



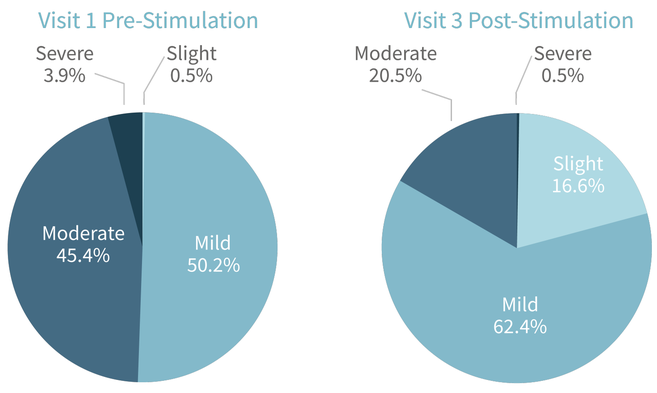
ADL Improvement Per In-Clinic Visit



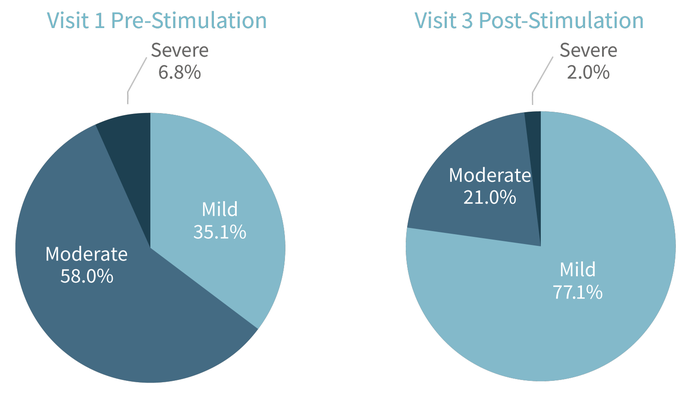
Primary Clinical Endpoint Improvements: Severity Group Changes

***Tremor severity subgroup classifications improved from the start to end of the study.** Physician-rated TETRAS dominant hand scores (left) were binned into Slight (0-6), Mild (7-12), Moderate (13-18), and Severe (19-24) categories per TETRAS guidelines. Patient-rated Bain & Findley ADL dominant hand score (right) were binned into Mild (9-16), Moderate (17-24), and Severe (25-32) categories per ADL guidelines. 62% (on TETRAS) and 68% (on ADL) of patients who were rated as 'Severe' or 'Moderate' at baseline pre-stimulation improved to 'Mild' or 'Slight' post-stimulation at the final in-clinic visit.*

TETRAS Dominant Hand Rating



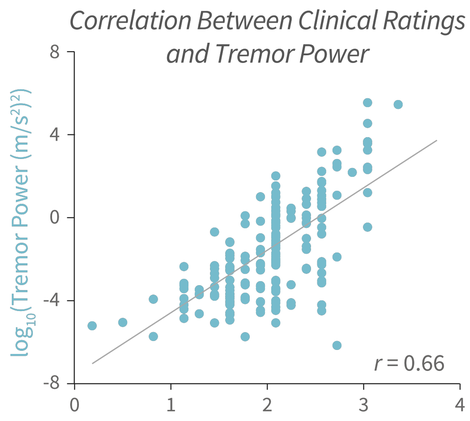
ADL Dominant Hand Rating



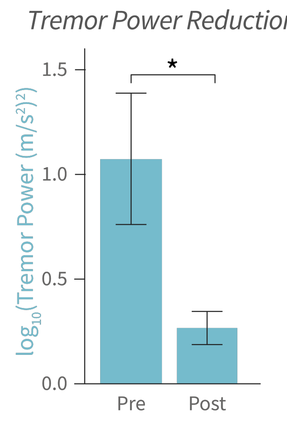
Device Accelerometer-Measured Tremor Kinematic Improvement

***Patients showed significant reductions in tremor power with therapy.** (Left) The clinician-rated TETRAS postural hold score was correlated (r=0.66, p<0.0001) to the tremor power measured from the device's onboard accelerometer during the baseline postural hold in the clinic (n = 193 patients), suggesting the sensor-data provide valuable at-home surrogate measures of clinical tremor rating. (Middle) Across the patient population, the average sensor-measured tremor power decreased after each at-home therapy session, compared to the pre-session value (n = 21,806 sessions, p < 0.0001). Error bars represent one standard error of the mean, and (*) indicates p<0.0001. (Right) Of the 193 analyzed patients, 92% showed median improvement in tremor power with therapy, and 54% experienced a median ≥2-fold (50%) improvement in tremor power.*

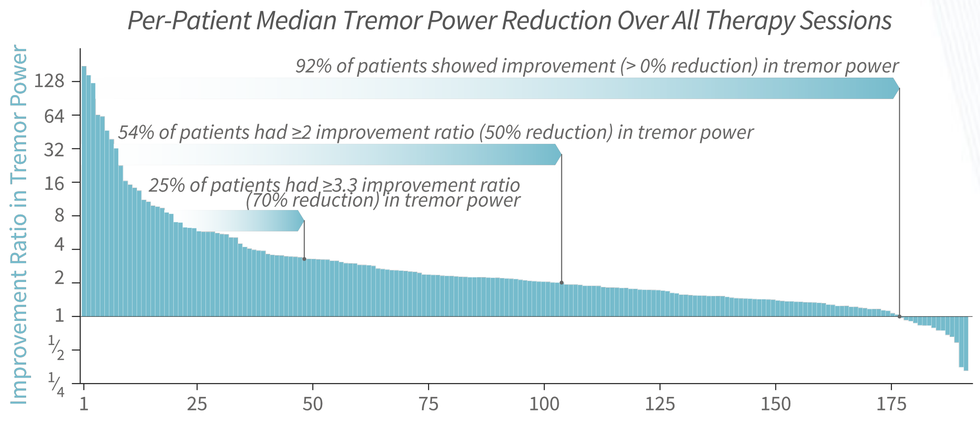
Correlation Between Clinical Ratings and Tremor Power



Tremor Power Reduction



Per-Patient Median Tremor Power Reduction Over All Therapy Sessions



Results

Patient age was 69.6 ± 10.1 years (23-89) (mean ± SD; range). Age of ET onset was 43.9 ± 20.4 (2-79). The study population was 52% female. Patients showed significant tremor improvement with device usage at each in-clinic visit. Pre-stimulation tremor severity improved across the three visits on both TETRAS (12.6 ± 0.2 at Visit 1 vs. 9.8 ± 0.2 at Visit 3; p<0.0001) and ADLs (18.4 6 ± 0.3 at Visit 1 vs. 15.8 ± 0.3 at Visit 3; p<0.0001), suggesting therapeutic usage led to a cumulative reduction in baseline tremor levels. Tremor powers measured by the devices' accelerometers were correlated (r = 0.66; p<0.0001) to the clinicians' TETRAS rating of the same postural hold, suggesting tremor power is an objective metric that could be collected at home to measure tremor severity. The mean $\log_{10}$-tremor power decreased from 1.1 ± 0.3 pre-stimulation to 0.3 ± 0.1 post-stimulation (p<0.0001) over all 21,806 stimulation sessions. Clinicians and patients reported improvement in tremor per the Clinical and Patient Global Impression of Improvement (CGI-I, PGI-I) scales, respectively. Patient survey results indicated 85% of patients found the device convenient and easy to use. 64% of patients reported persistent tremor relief lasting on average 96.7 ± 12 minutes (mean ± SEM) after a stimulation session. Quality of Life in Essential Tremor (QUEST) survey scores significantly improved at the conclusion of the study (p=0.001). Device-related adverse events occurred in 18% of patients, with no reported device-related serious adverse events.

Conclusions

This study demonstrated that noninvasive transcutaneous afferent patterned stimulation over a three-month period results in safe and effective reduction in hand tremor for essential tremor patients. Simultaneous measurements of clinical ratings and sensor-based measurements of tremor suggest objective metrics can be used to monitor treatment efficacy outside the clinic.

Clinical Trial Information*

The Prospective Study for Symptomatic Relief of Essential Tremor with Cala Therapy (PROSPECT) trial is registered with clinicaltrials.gov under identifier NCT03597100.

Acknowledgements

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