NEW RESEARCH

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Double-Blind, Sham-Controlled, Pilot Study of Trigeminal Nerve Stimulation for Attention-Deficit/Hyperactivity Disorder

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Objective: Trigeminal nerve stimulation (TNS), a minimal-risk noninvasive neuromodulation method, showed potential benefits for attention-deficit/hyperactivity disorder (ADHD) in an unblinded open study. The present blinded sham-controlled trial was conducted to assess the efficacy and safety of TNS for ADHD and potential changes in brain spectral power using resting-state quantitative electroencephalography.

Method: Sixty-two children 8 to 12 years old, with full-scale IQ of at least 85 and Schedule for Affective Disorders and Schizophrenia–diagnosed ADHD, were randomized to 4 weeks of nightly treatment with active or sham TNS, followed by 1 week without intervention. Assessments included weekly clinician-administered ADHD Rating Scales (ADHD-RS) and Clinical Global Impression (CGI) scales and quantitative electroencephalography at baseline and week 4.

Results: ADHD-RS total scores showed significant group-by-time interactions ($F_{1,228} = 8.12$, $p = .005$; week 4 Cohen $d = 0.5$). CGI-Improvement scores also favored active treatment ($\chi^2_{1,168} = 8.75$, $p = .003$; number needed to treat = 3). Resting-state quantitative electroencephalography showed increased spectral power in the right frontal and frontal midline frequency bands with active TNS. Neither group had clinically meaningful adverse events.

Conclusion: This study demonstrates TNS efficacy for ADHD in a blinded sham-controlled trial, with estimated treatment effect size similar to non-stimulants. TNS is well tolerated and has minimal risk. Additional research should examine treatment response durability and potential impact on brain development with sustained use.

Clinical trial registration information: Trigeminal Nerve Stimulation for ADHD; http://clinicaltrials.gov/; NCT02155608.

Key words: attention-deficit/hyperactivity disorder, clinical trial, neuromodulation, trigeminal nerve stimulation

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Although stimulant medications are regarded as the most effective and commonly used treatment for attention-deficit/hyperactivity disorder (ADHD),[1] side effect concerns, social stigma, and parental preferences for non-medication approaches contribute to a lack of long-term compliance.[2,3] In addition to standard psychosocial interventions such as parent management training and academic accommodations, there has been increasing interest in other non-medication approaches to ADHD, including electroencephalography (EEG)-based neurofeedback, computer-based working memory training, and noninvasive brain stimulation methods such as transcranial direct stimulation and transcranial magnetic stimulation. However, scientific studies of these modalities have largely failed to demonstrate positive effects.[4-8]

Trigeminal nerve stimulation (TNS) is a noninvasive minimal-risk neuromodulation method approved in Canada and Europe for adult treatment of medication-resistant major depression[9,10] and epilepsy.[11] Similar to the vagus nerve, the trigeminal nerve conveys sensory inputs from the skin, muscles, and skull to extensive connections within the locus coeruleus, reticular activating system, and nucleus tractus solitarius,[12] regions involved in selective maintenance of attention.[13] Recent data provide increased evidence that TNS exerts its effects through central projections to cortical structures.[14] TNS uses a small stimulator worn during sleep to emit a low-level current. Thin wires extend from the TNS device to an adhesive electrode worn across the forehead over branch V_1 of the trigeminal nerve. Assuming that benefits of vagal stimulation rely in part on the same brain connections, it was hypothesized that TNS

would similarly improve seizures and mood, but without the costs and risks associated with surgical device implantation.

Several TNS depression studies have suggested a potential role in ADHD. First, item analysis of mood rating scales showed that TNS was associated with selective improvements in concentration and attention (Ian Cook, personal communication). Second, a small positron-emission tomography study showed that acute TNS activated several brain regions implicated in ADHD and executive function, including the anterior cingulate cortex; inferior frontal, medial, and middle frontal gyri; and parietotemporal cortex.[15] Third, TNS is extremely well tolerated in adults and virtually without adverse events, suggesting suitability for pediatric testing.[16]

A preliminary open trial in ADHD-diagnosed youth suggested TNS was readily accepted by parents and children; associated with substantial decreases in parent and clinician ADHD symptom ratings and significant improvements on multiple indices of parent-reported executive functioning; and associated with dramatic improvements in laboratory measures of response inhibition.[17] Treatment was well tolerated and without meaningful adverse events.

The present study investigated the potential efficacy of TNS for ADHD treatment in a 4-week double-blinded sham-controlled trial followed by 1 blinded week without treatment to assess response persistence. This is the first blinded sham-controlled trial of TNS for ADHD or any pediatric condition. Secondary aims included assessment of cortical activation mechanisms, measured with quantitative EEG (qEEG), and effects on anxiety, mood, sleep, growth, and safety. The study further assessed time course effects, provided estimates of treatment effect sizes, and measured the success of blinding procedures in anticipation of future clinical trials.

METHOD

Participants

Participants were recruited through community advertisements and internet postings. Children 8 to 12 years old with *DSM-5* ADHD, based on the Schedule for Affective Disorders and Schizophrenia [18] and clinical interview, minimum total score of 24 on the clinician-administered parent ADHD-IV Rating Scale (ADHD-RS),[19] baseline Clinical Global Impression-Severity (CGI-S) score of at least 4,[20] estimated full-scale IQ of at least 85 based on Wechsler Abbreviated Scale of Intelligence subtests,[21] and able to cooperate with EEG and other study procedures were enrolled. Exclusion criteria were current major depression or autism spectrum disorder, lifetime psychosis, mania, seizure disorder, head injury with loss of consciousness, or baseline suicidality. Children were medication free for at least 1 month before participation and remained so throughout the trial. Before screening, parents and children received thorough verbal and written descriptions of study requirements and provided written permission and assent, respectively. The institutional review board of the University of California, Los Angeles, approved all study procedures.

Study Design

The study was a 4-week, double-blinded, sham-controlled trial, followed by 1 blinded week without intervention. Screening included diagnostic and IQ assessment,[18,21] clinician-completed parent ADHD-RS and CGI-S rating, parent-completed Childhood Behavioral Checklist,[22] and the parent- and child-rated Affective Reactivity Index (ARI).[23] Eligible participants returned at baseline for repeated clinician ratings, additional parent- and child-completed behavioral measures, computerized tests of executive function, and EEG. Randomization was 1:1, using random block lengths of 4 and 6, to active or sham TNS, with equal stratification on low ($\leq$6) or high parent ARI scores to assess potential effects on irritability. Families were taught proper electrode placement and device operation at baseline. Active or sham TNS was administered nightly during sleep. Participants returned after 1 week for repeated measurement of behavioral and cognitive outcomes and assessment of blinding integrity (Early Impressions Questionnaire; see below). Clinician and parent behavioral ratings were repeated weekly. After week 4, behavioral, cognitive, and EEG measures were repeated and treatment (active or sham) was discontinued. Participants and investigators remained blinded for 1 additional week when final behavioral and cognitive outcomes were repeated to assess potential benefit persistence after discontinuation.

TNS Intervention

TNS procedures were based on previous work in epilepsy,[11,24] adult depression,[9,10] posttraumatic stress disorder,[10] and ADHD.[17] Stimulation was performed with a CE-mark approved neurostimulator, the Monarch eTNS System (NeuroSigma, Inc., Los Angeles CA). The stimulator was worn on the child's pajamas or T-shirt and attached with thin wires to disposable, silver-gel, self-adhesive patch electrodes. Parents applied patches across their child's forehead to provide bilateral stimulation of V_1 trigeminal branches for approximately 8 hours nightly. Patches were removed each morning. The active condition used a 120-Hz repetition frequency, with 250-μs pulse width, and a duty cycle of 30 seconds on and 30 seconds

off. Stimulator current settings from 2 to 4 mA (range 0–10 mA) were established at baseline by titration, which identified a stimulation level below the participant's subjective level of discomfort. Power was provided by 9-V lithium medical-grade batteries (Energizer L522, Eveready Battery Co., St. Louis, MO), which were replaced every day.

Active and sham systems were identical in appearance and operation. Participants were informed at a scripted presentation that "pulses may come so fast or so slowly that the nerves in the forehead might or might not detect a sensation." Each night parents turned on the device, pressed the "up" button until the stimulation was uncomfortable or until the device reached the maximum current, and then pressed "down" to decrease it by 1 0.1-mA step. In active devices, current flowed to the patch and was limited to a safe range. Some, but not all, subjects in the active and sham groups reported feeling some sensation, which generally faded with time. With sham TNS, no current flowed, so participants adjusted settings without actually controlling current.

One research assistant who managed study devices had access to group assignments. All other staff, parents, and participants were blinded to randomized group. To assess study blinding effectiveness, parents completed the Early Impressions Questionnaire[25] after the initial treatment week to quantify expectations of success with their assigned condition.

Quantitative Electroencephalography

The qEEG acquisition followed previously used procedures.[26] Participants underwent qEEG recording, including a 5-minute eyes-open resting condition. Recordings were carried out using an Electrical Geodesics (Eugene, OR) GES300 system with 128-electrode high-impedance Hydrocel Geodesic Sensor Nets. Data were referenced to Cz, the impedance threshold was set at 50 kΩ (according to the manufacturer's standard), and sampling rate was 1,000 Hz. Eye movements were monitored by electrodes placed on the outer canthus of each eye for horizontal movements (right and left electrooculograms) and by electrodes above the eyes for vertical eye movements. Key head landmarks (nasion, inion, preauricular notches) and 3-dimensional electrode locations were recorded (Polhemus, Inc., Colchester, VT) to allow 3-dimensional reconstruction of scalp electrode positions.

Continuous EEG data were imported into the EEGLAB environment for processing.[27] The EEG data were high-pass filtered (>1 Hz), re-referenced to the channel average, rejected for excessive noise, and decomposed using independent components analysis, which separates brain from non-brain (eg, muscle, eye) artifacts that contribute to scalp-recorded signals. Independent components were inspected for spatial, spectral, and temporal properties to identify those with patterns corresponding to non-brain sources of signal such as eye blinks, lateral eye movement, cardiac artifacts, single-channel artifacts, and high-frequency line noise; these components were excluded from further analyses. Cleaned data were back-projected into channel space for resting-state analyses. Fourier transform was used to estimate spectral power in frequencies from 1 to 50 Hz for channels F3/4, Fz, C3/4, Cz, P3/4, and Pz and averaged across standard frequency bands (delta, 1–3 Hz; theta, 4–7 Hz; alpha, 8–12 Hz; beta 1, 13–16 Hz; beta 2, 17–25 Hz; gamma 1, 30–40 Hz; gamma 2, 40–50 Hz).

Outcome Measures

The primary efficacy outcome measure was the clinician-completed ADHD-RS total score,[19] based on parental interview and all available clinical information, completed at baseline and over subsequent weeks. Secondary behavioral outcomes included weekly clinician-scored CGI-Improvement (CGI-I) scales,[20] weekly parent-completed Behavioral Rating Inventory of Executive Functioning (BRIEF) scales,[28] Conners Global Index,[29] Children's Sleep Habits Questionnaire (CSHQ),[30] and teacher-completed Conners Global Index.[29] Ratings at baseline and weeks 4 and 5 included the parent- and child-completed ARI and Multidimensional Anxiety Scale for Children (MASC)[31] and the clinician-completed Children's Depression Rating Scale (CDRS-R).[32] Secondary cognitive outcomes included the computer-based Spatial Working Memory Test[33] and Attention Network Task[34] at baseline and weeks 1, 4, and 5. The qEEG was conducted at baseline and weeks 1 and 4. Cognitive outcomes will be presented in a subsequent publication addressing neurobiological response mechanisms. Safety was assessed by height, weight, and vital sign measurements at each clinic visit, and weekly open-ended adverse event inquiries, parent-completed Side Effects Rating Scales,[17] and clinician-completed Columbia Suicide Severity Rating Scales (C-SSRS).[35]

Statistical Analysis

All analyses were conducted in SAS 9.4 (SAS Institute, Cary, NC). To confirm successful randomization, we compared groups on baseline demographic and clinical characteristics using t tests and χ^2 tests as appropriate. Subsequently, data were assessed for normality and sphericity and outcome variables were plotted as a function of time to determine forms of treatment trajectories (eg, linear, quadratic, piecewise linear with change of slope, etc.).

Our primary analytic tool was the general linear mixed model with treatment group (active versus sham), time (in

weeks), and group-by-time interactions to test for differential treatment effects as primary predictors, along with subject level random intercepts. General linear mixed models properly account for correlations induced by repeated measurements within subjects and automatically handle missing values, allowing maximum use of available data. As such, all participants with baseline data were included in analyses. We fitted a single model for each dimensional outcome from baseline to the end of the 4 weeks. Separate models were fit for the blinded discontinuation period between weeks 4 and 5.

Categorical outcomes were assessed using χ^2 test. For CGI-I, a binary variable was created in which scores of 1 or 2 (very much improved or much improved) were deemed "improved" and scores higher than 2 were considered "not improved." CGI-I score was determined weekly in reference to baseline. Adverse event frequencies within each group were tallied over the study course based on the Side Effects Rating Scale and spontaneous report. Likert scale values from the Early Impression Questionnaire were assessed by logistic regression as predictive of treatment group to assess validity of blinding procedures. Effect size differences between groups were estimated using Cohen *d* and number needed to treat. For Cohen *d*, cutoff values for small, medium, and large effects were defined as 0.2, 0.5, and 0.8, respectively.[36] For number needed to treat, small, medium, and large effects were defined as 9, 4, and 2, respectively.[37]

Effects of multiple testing were minimized by identifying the ADHD-RS total score a priori as the single primary outcome. However, for a developmental pilot, the identification of sensitive outcomes and protocol parameters carried more importance for future research design than minimizing type I error. Therefore, all results are reported using an uncorrected significance α level equal to .05.

RESULTS

Demographics and Disposition

Of 79 individuals screened, 62 were eligible and randomized to active (n = 32) or sham (n = 30) TNS. Of those ineligible, 13 did not meet the inclusion criteria, 2 met the exclusion criteria, and 2 did not return after initial screening. One participant randomized to sham TNS left the trial after week 3. One additional participant in each group withdrew between weeks 4 and 5. The qEEG data for 3 participants were excluded because of excessive movement artifact, leaving 56 participants (active, n = 30; sham, n = 26) for EEG analyses. Participant characteristics are presented in Table 1. No significant group differences were found for age, sex, race/ethnicity, height, weight, vital signs, IQ, ADHD subtype, or baseline behavioral ratings.

Efficacy Measures

Initial analyses demonstrated that dependent variables were normally distributed and that assumptions of sphericity were not violated. Plotted ADHD-RS total scores over time suggested a nonlinear pattern, with decreasing scores in the 2 groups during the first week, followed by ongoing improvement, albeit slower, in the active group versus a flattening response trajectory in the sham group (Figure 1). In consequence, dimensional behavioral outcomes were fitted using a mixed-effects model with group-by-time interactions to test for treatment effects using a piecewise linear time trend. This was parameterized in the model as a standard linear variable, time (ranging from baseline to 4 weeks), and a second variable, time2, defined as 0 at baseline and time past week 1 for subsequent weeks. The time2 coefficient represents the change in slope after the initial week. Height, weight, and vital signs demonstrated linear patterns and were evaluated using time only, as were measures taken only at baseline and week 4.

ADHD-RS total scores showed a significant group-by-time interaction, demonstrating a differential treatment effect ($F_{1,228} = 8.12$, $p = .005$). The significant main effect of time ($F_{1,228} = 39.97$, $p < .0001$) showed initial improvement in the 2 groups, which was greater with active TNS. Time2 also showed a significant effect ($F_{1,228} = 28.96$, $p < .0001$), but no group-by-time2 interaction, indicating an equal leveling off of improvement after week 1. Estimated Cohen *d* at week 4 was 0.50, suggesting a medium-size treatment effect. CGI-I scores over the 4-week course similarly favored active over sham TNS ($\chi^2_{1,168} = 8.75$, $p = .003$). Improvement rates for active versus sham TNS were 25% versus 13%, 34% versus 15%, 47% versus 12%, and 52% versus 14% based on raw CGI-I scores at weeks 1, 2, 3, and 4, respectively, with a trend for increasing improvement with active TNS over time ($\chi^2_{3,168} = 5.08$, $p = .17$). Number needed to treat based on CGI-I score at week 4 was 3.

Table S1, available online, presents other exploratory outcomes with significant effects. The same pattern of time, time2, and group-by-time effects was found with the Inattentive and Hyperactive-Impulsive ADHD-RS subscales as with total scores. A similar piecewise linear trajectory, but no group or interactive effects, was seen with the parent-completed Conners Global Index. The MASC parent report showed trends for time ($F_{1,53} = 3.58$, $p = .06$) and group-by-time ($F_{1,53} = 2.90$, $p = .09$) effects (estimated Cohen $d = 0.33$). The CSHQ score showed significant time and time2 effects, but no group-by-time interactions, for bedtime resistance, sleep anxiety, and total sleep problems. Other behavioral outcomes, including the MASC child

TABLE 1 Participant Characteristics at Baseline by Assigned Treatment Group[a]

	Total Sample (N = 62)	Active Group (n = 32)	Sham Group (n = 30)
Age (y), mean (SD)	10.4 (1.4)	10.3 (1.4)	10.5 (1.4)
Boys, n (%)	40 (65)	19 (60)	21 (70)
Race/ethnicity, n (%)			
White	40 (65)	20 (63)	20 (67)
Black	4 (6)	4 (13)	0
Asian	10 (16)	5 (16)	5 (17)
Mixed/other	8 (13)	3 (9)	5 (17)
Hispanic	10 (16)	5 (16)	5 (17)
Height (cm), mean (SD)	142.2 (9.9)	142.8 (10.1)	141.5 (9.9)
Weight (kg), mean (SD)	37.1 (10.5)	38.8 (12.3)	35.4 (8.1)
Systolic BP, mean (SD)	107 (11.8)	108.5 (11.53)	106.2 (12.2)
Diastolic BP, mean (SD)	64.3 (7.9)	65.0 (8.2)	63.6 (7.6)
Pulse, mean (SD)	76.7 (11.6)	71.7 (9.2)	76.6 (13.1)
Full-scale IQ, mean (SD)	108.9 (13.2)	110.4 (12.3)	107.3 (14.2)
ADHD subtype, n (%)			
Combined	39 (63)	22 (69)	17 (57)
Inattentive	21 (34)	9 (28)	12 (40)
Hyperactive/ impulsive	2 (3)	1 (3)	1 (3)
Comorbidity, n (%)			
ODD	20 (32)	11 (34)	9 (30)
DMDD	17 (27)	10 (31)	7 (23)
Social phobia	10 (16)	7 (21)	3 (10)
Separation anxiety	2 (3)	1 (3)	1 (3)
Generalized anxiety	10 (16)	6 (19)	4 (13)
Any anxiety	18 (29)	11 (3)	7 (23)
Enuresis	6 (12)	5 (16)	1 (3)
Encopresis	2 (3)	0	2 (7)
Tourette's disorder	2 (3)	2 (6)	0
Motor tic	1 (2)	0	1 (3)
ADHD-RS-T, mean (SD)	32.5 (6.2)	32.1 (6.3)	32.8 (6.2)
ARI-P score, mean (SD)	4.5 (3.7)	4.4 (3.9)	4.5 (3.9)
MASC—child score, mean (SD)	60.6 (25.7)	59.0 (26.2)	62.4 (25.5)
MASC—parent score, mean (SD)	47.4 (19.2)	46.2 (19.2)	48.7 (19.2)
CDRS-R score, mean (SD)	9.71 (6.4)	10.4 (6.9)	9.0 (5.8)
CGI-S score, n (%)			
4	21 (34)	10 (31)	11 (37)
5	41 (66)	22 (69)	19 (63)

***Note**: ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-T = Attention-Deficit/Hyperactivity Disorder Rating Scale Total Score; ARI-P = Affective Reactivity Index—Parent Report; BP = blood pressure; CDRS-R = Children's Depression Rating Scale; CGI-S = Clinical Global Impression Severity Scale; cm = centimeters; DMDD = disruptive mood dysregulation disorder; kg = kilograms; MASC = Manifest Anxiety Scale for Children; ODD = oppositional defiant disorder.*

[a]*No significant differences between groups (p > .05 for all comparisons).*

report, CDRS-R, BRIEF, remaining CSHQ scales, teacher Conners Global Index, and ARI scales, were not significant.

With resting-state qEEG, active TNS demonstrated increased broadband power, whereas sham TNS exhibited decreased power, in the right frontal region (Figure 2). Treatment groups did not differ at any channel or frequency band at baseline ($p > .3$ for all comparisons). EEG spectral power statistics are presented in Table S2, available online, and showed significant group-by-time effects for frequency bands in the right frontal (F4 delta, theta, beta, gamma) and frontal midline (Fz gamma) channels, with trend level effects for frequency bands in the midfrontal region (Fz delta, theta, beta). Left frontal region (F3) effects were generally in the same direction but did not reach significance ($p > .2$ for all comparisons). No significant group, time, or group-by-time effects were seen in central or parietal electrodes ($p > .2$ for all comparisons).

To facilitate functional interpretation of qEEG changes, significant EEG outcomes and ADHD behavioral ratings were evaluated using Pearson partial correlations with age as a covariate. Week 4 changes in right frontal (F4 theta, beta bands) and frontal midline (Fz gamma 1) regions were significantly associated with changes in ADHD-RS total and hyperactive/impulsive scores (r −0.34 to −0.41; Table S3, available online). Spectral power changes had weaker correlations with inattentive symptoms and none were statistically significant ($p > .13$ for all comparisons). These correlations suggest that treatment-related spectral power increases in frontal midline and right frontal regions were associated with lower ADHD-RS scores, particularly hyperactive-impulsive scores, at trial end.

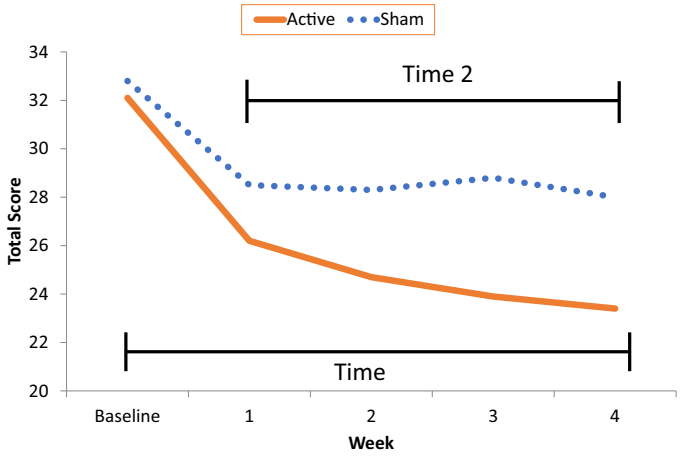
Discontinuation Outcomes

ADHD-RS total scores worsened in the 2 groups between weeks 4 and 5 after treatment discontinuation. Week 4 mean scores for the active and sham groups were 23.39 (standard deviation [SD] 7.88) and 27.50 (SD 8.08), respectively, and week 5 scores were 25.52 (SD 7.84) and 29.11 (SD 7.79). Time effect was significant ($F_{1,57} = 6.23$, $p = .02$), with a trend for group differences ($F_{1,57} = 4.18$, $p = .05$), but no significant group-by-time interaction ($F_{1,57} = 0.12$, $p = .73$), suggesting the 2 groups showed similar deterioration rates. Week 5 CGI-I ratings showed 13% versus 7% improvement in the active versus sham groups compared with baseline ($\chi^2_1 = 0.53$, $p = .46$; week 5 Cohen $d = 0.46$), suggesting maintenance of a medium-size treatment effect 1 week after treatment cessation.

Safety and Tolerability

Significant increases in weight and pulse were seen with active compared with sham TNS over 4 weeks, but there

FIGURE 1 Attention-Deficit/Hyperactivity Disorder Rating Scale Total Scores Over 4-Week Blinded Trial: Active Versus Sham Trigeminal Nerve Stimulation



were no group differences in increased height or blood pressure (Table 2). There were no serious adverse events in either group and no participant withdrew for adverse events. C-SSRS scores showed no responses suggestive of suicidality. Side Effects Rating Scale responses are presented in Table 3, with notable increases in fatigue, headache, and increased appetite with active TNS and increased hyperactivity with sham TNS. Table S4, available online, presents spontaneously reported adverse events. One initially concerning adverse event, skin whitening/discoloration under the patch site in some darker-skinned participants, occurred in active and sham groups and was attributed to patch removal and concomitant loss of superficial skin layers. Skin discoloration resolved with subsequent sun exposure and time.

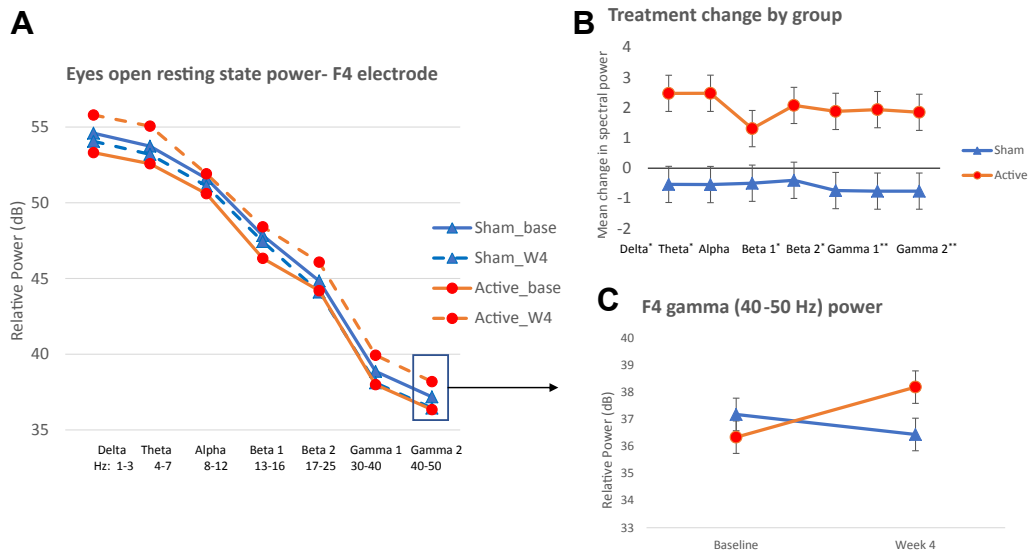
Assessment of Study Blinding

Responses on the Early Impressions Questionnaire showed no differences predictive of group assignment on questions pertaining to belief in having an active or sham device: how successful do you think your current treatment will be in decreasing ADHD symptoms (odds ratio 0.93, 95% CI 0.76–1.15, $p = .50$) or how much do you feel the current treatment will help decrease ADHD symptoms (odds ratio 0.90, 95% CI = 0.70–1.14, $p = .37$).

DISCUSSION

This study demonstrated the efficacy and safety of TNS in ADHD treatment, confirming and expanding previous open-label findings.[17] ADHD-RS response patterns suggest that the greatest degree of TNS-related improvement occurs during the first week, with additional improvement accruing with ongoing use. The week 4 medium-sized treatment effect is within the same range typically evidenced with non-stimulant ADHD medications.[38] Weekly CGI-I ratings

FIGURE 2 Treatment-Related Change in Electroencephalography Spectral Power at F4 Electrode



Note: *(A) During eyes-open resting state, active trigeminal nerve stimulation treatment was associated with increased broadband spectral power from baseline to week 4 (orange solid and dashed lines, respectively) compared with sham treatment, which showed no change or slight decrease from baseline to week 4 (blue solid and dashed lines, respectively), particularly in the right frontal region. (B) Amount of change for each treatment group in the active and sham trigeminal nerve stimulation groups suggests increased power in the active group and decreased power in the sham group across multiple frequency bands. (C) Depiction of significant group-by-time interaction effect for F4 gamma power; data for other frequency bands and Fz electrode show similar patterns. Base = baseline, W4 = week4 treatment end.*
*$p < .05$; **$p < .01$.

TABLE 2 Vital Sign Changes During Double Blind: Active Versus Sham Trigeminal Nerve Stimulation

	Active				Sham							
	Visit 0		Visit 4		Visit 0		Visit 4					
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Effect	*F*	*df*	*p*
Height (cm)	142.8	10.1	143.1	10.0	141.5	9.9	142.3	9.8	group	<1	1, 229	.59
									time	**5.83**	**1, 229**	**.02**
									group × time	1.03	1, 229	.31
Weight (kg)	38.8	12.3	39.7	10.5	35.4	8.1	35.7	10.3	group	1.62	1, 128	.21
									time	**5.18**	**1, 128**	**.02**
									group × time	**6.89**	**1, 128**	**.01**
Pulse (beats/min)	71.7	9.2	81.8	12.7	76.6	13.1	75.2	12.6	group	<1	1, 128	.79
									time	1.10	1, 128	.30
									group × time	**4.61**	**1, 128**	**.03**
Systolic BP	108.5	11.5	111.0	12.7	106.2	12.2	107.8	12.5	group	<1	1, 128	.93
									time	<1	1, 122	.76
									group × time	<1	1, 128	.39
Diastolic BP	65.0	8.2	65.1	9.3	63.6	7.6	61.0	9.2	group	<1	1, 128	.64
									time	1.75	1, 128	.19
									group × time	1.49	1, 128	.22

Note: *Boldface type indicates significance at* $p < .05$. *BP = blood pressure; cm = centimeters; df = degrees of freedom; kg = kilograms.*

further indicate that response rates increase with sustained treatment, at least over 4 weeks. Worsening scores over the discontinuation week likely reflect in part an awareness of treatment cessation in the 2 groups. However, even with the parallel decreases in score, lower active ADHD-RS scores at week 5 compared with the sham group suggest some persistent benefit after treatment discontinuation. Together, these results support the utility of TNS as a component of clinical ADHD management.

At a mechanistic level, TNS is believed to stimulate the nucleus tractus solitarius, which relays signals to cortical and subcortical structures such as the thalamus, hypothalamus, amygdala, locus coeruleus, reticular activating system, anterior cingulate, and insula.[12,14,17] Treatment-related changes in resting-state qEEG measures suggest that middle and right frontal regions show increased activation with active compared with sham TNS. Furthermore, these changes are primarily associated with improvement in hyperactive and impulsive symptom changes. Previous scalp qEEG studies reported increased power in delta, theta, and beta frequency bands at right frontal electrodes with successful stopping within a stop signal task,[39,40] suggesting a significant association between the right frontal cortex and inhibitory control. The right inferior frontal cortex,

TABLE 3 Percentage of Participants Endorsing Side Effects on Rating Scale at Some Point During 4-Week Blinded Trial: Active Versus Sham Trigeminal Nerve Stimulation

Side Effect (% Reporting)	Active (n = 32)	Sham (n = 30)	Side Effect (% Reporting)	Active (n = 32)	Sham (n = 30)
Trouble sleeping	19	17	Rapid heartbeat	3	0
Nightmares	6	0	Out of breath	3	3
Drowsy	22	13	Nausea	3	0
Hyperactive	41	63	Stomachache	6	3
Fatigue	13	3	Constipation	9	7
Feels strange	0	7	Frequent urination	6	0
Tingling	3	0	Frequent sweating	3	3
Headache	13	0	Decreased appetite	3	3
Stuffy nose	16	20	Increased appetite	19	7
Muscle cramps	3	3	Skin rash	6	0
Muscle twitch	0	7	Finding words	0	7
Tremor	0	3	Apathy	6	7
Slurred speech	0	3	Clenching teeth	13	7

pre-supplemental motor area, and subthalamic nuclei are believed to be part of a frontobasal ganglia network used in suppression of motor behavior.[41] Taken together, we hypothesize that the neurophysiologic mechanism underlying TNS treatment effects in ADHD is activation of the frontobasal ganglia network, resulting in increased EEG power in middle and right frontal electrodes and subsequent improvement in hyperactive and impulsive behaviors.

Many studies of non-medication ADHD treatments are biased toward false positive findings, particularly when blinding is compromised or raters are highly invested in treatment success.[42] Results from the Early Impressions Questionnaire showed no differences in outcome expectations between treatment groups after 1 week using the randomized device, suggesting that our sham procedures successfully accomplished double blinding of group assignment. Improvements seen in the active and sham groups at week 1 likely reflect some placebo response secondary to the high level of parental involvement in administering treatment. Nonetheless, further improvement over subsequent weeks with active TNS suggests the emergence of true treatment effects, demonstrated in clinician-rated ADHD-RS and CGI-I scores. In contrast, parent Conners Global Index ratings show significant time effects in the 2 groups, but no group-by-treatment differences, likely due to some placebo response among all raters. EEG findings, which demonstrated clear treatment-related differences in cortical activation, provide independent verification of positive behavioral outcomes unbiased by rater expectations. Small but measurable TNS effects on parent-reported anxiety provide further evidence of positive response.

As with previous reports, results confirm that TNS carries minimal risk and is well tolerated and accepted by ADHD-affected children and their parents.[17] Adverse events had minimal clinical significance. Although reports of headache and fatigue were associated with active TNS, no one abandoned treatment because of side effects. Increases in weight and reported appetite in the active group are not readily explained and require ongoing investigation in longer studies.

The potential significance of observed increased heart rate with active TNS remains unclear. Prior acute studies of TNS have shown increases[17] and decreases[14] in pulse. As with the vagus nerve, TNS is known to elicit parasympathetic activity, which is expected to result in pulse decreases or bradycardia.[43] Pulse increases in this study, although statistically significant, were not within a clinically abnormal range and were not associated with clinical symptoms. ADHD stimulants also are associated with small increases in heart rate that are not viewed as clinically meaningful. Results derived from this small sample also might represent outlier findings not generalizable to larger groups. The issue clearly requires further investigation but is not inconsistent with the assertion that TNS poses minimal risk.

The study assessed acute response to TNS over 4 weeks. It does not inform on whether additional improvement would accrue with ongoing treatment or whether benefits persist over time. There might have been some bias toward non-medication approaches to ADHD management by parents of study participants, but this view is common among many parents seeking ADHD treatment for their children. As such, results from this study should be widely generalizable, but support for TNS would be strengthened if replicated in additional patient groups. We did not assess potential utility of TNS as adjunctive therapy to standard ADHD interventions. The study failed to support several hypotheses arising from the open-label trial, particularly positive benefits seen in executive functioning, measured by the BRIEF, and selected sleep measures, measured by the CSHQ. However, because mean ratings on these measures were subclinical, it is unknown whether improvement might be evidenced if limited to those individuals with clinically significant difficulties. These relations require additional analysis.

TNS is a non-medication minimal risk intervention with proven efficacy in alleviating ADHD symptoms. Although the present study finds that only slightly more than half of those receiving therapy have clinically meaningful improvement, the virtual lack of significant side effects should make it a popular treatment choice for many patients with ADHD, particularly for parents who prefer to avoid psychotropic medication. The quality of evidence for TNS exceeds that which is available for many commercially available complementary interventions. TNS is potentially a valuable new addition to the ADHD treatment armamentarium.

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Drs. McGough, Loo, and Sugar served as the statistical experts for this research.

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REFERENCES

1. Danielson ML, Visser SN, Chroni-Tuscano A, DuPaul GJ. A national description of treatment among United States children and adolescent with attention-deficit/hyperactivity disorder. J Pediatr. 2018;192:240-246.
2. Brinkman WB, Simon JO, Epstein JN. Reasons why children and adolescent with attention-deficit/hyperactive disorder stop and restart taking medicine. Acad Pediatr. 2018;18:273-280.
3. Coletti DJ, Pappadopulos E, Katsiotas NJ, Berest A, Jensen PS, Kafantaris V. Parent perspectives on the decision to initiate medication treatment of attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2012;22:226-237.
4. Cortese S, Ferrn M, Brandeis D, *et al*. Neurofeedback for attention-deficit/hyperactivity disorder: meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials. J Am Acad Child Adolesc Psychiatry. 2016;55:444-455.
5. Cortese S, Ferrn M, Brandeis D, *et al*. Cognitive training for attention-deficit/hyperactivity disorder: meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials. J Am Acad Child Adolesc Psychiatry. 2015;54:164-174.
6. Cosmo C, Baptista AF, deAraújo AN, *et al*. A randomized, double-blind, sham-controlled trial of transcranial direct current stimulation in attention-deficit/hyperactivity disorder. PLoS One. 2015;10:e0135371.
7. Rubio B, Boes AD, Laganiere S, Rotenberg A, Jeurissen D, Pascual-Leone A. Noninvasive brain stimulation in pediatric ADHD: a review. J Child Neurol. 2016;31:784-796.
8. Weaver L, Rostain AL, Mace W, Akhtar U, Moss E, O'Reardon JP. Transcranial magnetic stimulation (TMS) in the treatment of attention-deficit/hyperactivity disorder. J ECT. 2012;28:98-103.
9. Schrader LM, Cook IA, Miller PR, Maremont ER, DiGiorgio CM. Trigeminal nerve stimulation in major depressive disorder: first proof of concept in an open pilot trial. Epilepsy Behav. 2011;22:475-478.
10. Cook IA, Abrams M, Leuchter AF. Trigeminal nerve stimulation for comorbid posttraumatic stress disorder and major depressive disorder. Neuromodulation. 2016;19:299-305.
11. Cook AI, Kealey CP, DeGiorgio CM. The potential use of trigeminal nerve stimulation in the treatment of epilepsy. Ther Deliv. 2015;6:273-275.
12. Nolte J. The Human Brain: An Introduction to Its Functional Anatomy. 4th ed. St Louis, MO: Elsevier; 1999.
13. Peterson SE, Posner MI. The attention system of the human brain: 20 years after. Annu Rev Neurosci. 2012;35:73-89.
14. Mercante B, Enrico P, Floris G, *et al*. Trigeminal nerve stimulation induces FOS immunoreactivity in selected brain regions, increased hippocampal cell proliferation and reduces seizure severity in rats. Neuroscience. 2017;361:69-80.
15. Cook IA, Espinoza R, Leuchter AF. Neuromodulation for depression: invasive and noninvasive (deep brain stimulation, transcranial magnetic stimulation, trigeminal nerve stimulation). Neurosurg Clin North Am. 2014;25:103-116.
16. DeGiorgio CM, Fanselow EE, Schrader LM, Cook IA. Trigeminal nerve stimulation: seminal animal and human studies for epilepsy and depression. Neurosurg Clin North Am. 2011;22:449-456.
17. McGough JJ, Loo SK, Sturm A, Cowen J, Leuchter AF, Cook IA. An eight-week, open-trial, pilot feasibility study of trigeminal nerve stimulant in youth with attention-deficit/hyperactivity disorder. Brain Stimul. 2015;8:299-304.
18. Kaufman J, Birmaher B, Brent D, *et al*. Schedule for Affective Disorders and Schizophrenia for School Aged Children—Present and Lifetime Version (K-SADS-PL). J Am Acad Child Adolesc Psychiatry. 1997;36:980-988.
19. DuPaul GJ, Power RJ, Anastopoulos AD, Reid R. ADHD Rating Scale-IV Checklist, Norms and Clinical Interpretations. New York: Guilford Press; 1998.
20. Guy W. EDCEU Assessment Manual for Psychopharmacology (Revised). Washington, DC: US Department of Health, Education, and Welfare; 1976.
21. Wechsler D. Wechsler Abbreviated Scale of Intelligence. 3rd ed. London: Pearson Education; 1997.
22. Achenbach TM. Manual for the Child Behavior Checklist/4-18. Burlington: University of Vermont, Department of Psychiatry; 1999.
23. Stringaris A, Goodman R, Ferdinando S, *et al*. The Affective Reactivity Index: a concise irritability scale. J Child Psychol Psychiatry. 2012;53:1109-1117.
24. DeGiorgio CM, Soss J, Cook IA, *et al*. Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy. Neurology. 2013;80:786-791.
25. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. J Beh Ther Exp Psychiatry. 2000;31:73-86.
26. Loo SK, Bilder RM, Cho AL, *et al*. Effects of d-methylphenidate, guanfacine, and their combination on electroencephalogram resting state spectral power in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2016;55:674-682.
27. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods. 2004;134:9-21.
28. Gioia GA, Isquith PK, Guy SC, Kenworthy L. Test review: Behavior Rating Inventory of Executive Functioning. Child Neuropsychology. 2000;6:235-238.
29. Conners CK. Conners' Global Index. Toronto, Canada: Multi-Health Systems; 1997.
30. Owens JA, Spiritio A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep. 2000;15:1043-1051.
31. March J. Multidimensional Anxiety Scale for Children. Toronto, Canada: Multi-Health Systems; 1997.
32. Poznanski EO, Freeman LN, Mokros HB. Children's Depression Rating Scale—Revised. Psychopharmacol Bull. 1985;21:979-989.
33. Glahn DC, Kim J, Cohen MS, *et al*. Maintenance and manipulation in spatial working memory: dissociations in the prefrontal cortex. Neuroimage. 2002;17:201-213.
34. Fan J, Wu Y, Fossella JA, Posner MI. Assessing the heritability of attentional networks. BMC Neurosci. 2001;2:14.
35. Posner K, Brown GK, Stanley B, *et al*. Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168:1266-1277.
36. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Mahwah, NJ: Lawrence Erlbaum Associates; 1988.
37. Kramer HC, Kupfer DJ. Size of treatment effects and their importance to clinical research and practice. Biol Psychiatry. 2006;59:990-996.
38. Faraone SV, Biederman J, Spencer TJ, Aleardi M. Comparing the efficacy of medications for ADHD using meta-analysis. MedGenMed. 2006;8:4.
39. Huster RJ, Enriquez-Geppert S, Lavalle CF, Falkenstein M, Herrmann CS. Electroencephalography of response inhibition tasks: functional networks and cognitive contributions. Int J Psychophysiol. 2013;87:217-233.
40. Wagner J, Wessel J, Gharahmeni A, Aron A. Establishing a right frontal beta signature for stopping active in scalp electroencephalography: implications for testing inhibitory control in other task contexts. J Cognitive Neuroscience. 2018;1:107-118.
41. Wessel JR, Aron AR. On the globality of motor suppression: unexpected events and their influence on behavior and cognition. Neuron. 2017;93:259-280.
42. Sonuga-Barke EJ, Brandeis D, Cortese S, *et al*. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. Am J Psychiatry. 2013;170:275-289.
43. Kumada M, Dampney RA, Reis DJ. The trigeminal depressor response: a novel vasodepressor response originating from the trigeminal system. Brain Res. 177;119:305-326.

TABLE S1 Secondary Efficacy Measures With Significant Effects for Double-Blind Active Versus Sham Trigeminal Nerve Stimulation

Measure	Effect	*F*	*df*	*p*
ADHD-RS Inattentive subscale	group	<1	1, 228	.55
	time	34.30	1, 228	**<.0001**
	time2	23.20	1, 228	**<.0001**
	group × time	5.35	1, 228	**.02**
ADHD-RS Hyperactive/Impulsive subscale	group	<1	1, 228	.62
	time	29.28	1, 228	**<.0001**
	time2	23.02	1, 228	**<.0001**
	group × time	7.83	1, 228	**.007**
Conners Global Index parent report	group	.01	1, 209	.91
	time	13.03	1, 209	**.0004**
	time2	7.45	1, 209	**.007**
	group × time	<1	1, 209	.36
CSHQ Bedtime Resistance subscale	group	<1	1, 205	.51
	time	6.12	1, 205	**.01**
	time2	2.75	1, 205	.10
	group × time	<1	1, 205	.50
CSHQ Sleep Anxiety subscale	group	<1	1, 202	.33
	time	11.48	1, 202	**.0008**
	time2	5.81	1, 202	**.02**
	group × time	<1	1, 202	.94
CSHQ Total Sleep Problems subscale	group	2.04	1, 183	.16
	time	14.36	1, 183	**.0002**
	time2	6.18	1, 183	**.01**
	group × time	1.48	1, 183	.23
MASC parent report	group	0.25	1, 53	.62
	time	3.58	1, 53	*.06*
	group × time	2.90	1, 53	*.09*

***Note**: Boldface type indicates significance at* $p < .05$. *Italic type indicates trend level effects at* $p < .10$. *ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale; CSHQ = Children's Sleep Health Questionnaire; df = degrees of freedom; MASC = Manifest Anxiety Scale for Children.*

TABLE S2 Summary of *F* Values for Treatment Effects on Resting State Electroencephalographic Spectral Power

Frequency Band	Electrode	Group	Time	Group × Time
Delta	F3	<1	<1	1.13
	F4	<1	2.5	5.9*
	Fz	<1	<1	*2.9*
	C3	<1	<1	1
	C4	<1	1.1	1.1
	Cz	<1	<1	1
	P3	<1	<1	<1
	P4	<1	<1	1.3
	Pz	<1	<1	<1
Theta	F3	<1	<1	1
	F4	<1	2.6	6.2*
	Fz	<1	1.1	*2.9*
	C3	<1	<1	<1
	C4	<1	<1	<1
	Cz	<1	<1	<1
	P3	<1	1.1	<1
	P4	<1	<1	<1
	Pz	<1	<1	<1
Beta 1, 2	F3	<1, <1	<1, <1	<1, <1
	F4	<1, <1	2.4, 1.2	5.2*, 6.0*
	Fz	<1, <1	<1, <1	*3.3, 3.3*
	C3	<1, 1.5	1.5, 1.9	<1, <1
	C4	<1, <1	<1, <1	<1, <1
	Cz	<1, 1	<1, <1	<1, <1
	P3	<1, 1	2.6, 2.2	<1, <1
	P4	<1, <1	<1, <1	<1, <1
	Pz	<1, 1.7	<1, <1	<1, <1
Gamma 1, 2	F3	<1, <1	<1, <1	<1, <1
	F4	<1, <1	1.4, 1.2	7.1**, 6.5**
	Fz	<1, <1	<1, <1	4*, *3.8*
	C3	1.2, <1	1.1, <1	1.2
	C4	<1, <1	<1, <1	1, <1
	Cz	1.6, 1.9	<1, <1	1.2, 1.1
	P3	2, 2.2	1.3, <1	<1, <1
	P4	<1, <1	<1, <1	1.6, 1
	Pz	3.5, *3.7*	<1, <1	<1, <1

***Note**: For all analyses, degrees of freedom are 1, 47–70. No significant effects were found in the alpha band. Italic type indicates trend level effects at p < .10. Beta 1 = 13–16 Hz; Beta 2 = 17–25 Hz; C = central; Delta = 1–3 Hz; F = frontal; Gamma 1 = 30–40 Hz; Gamma 2 = 40–50 Hz; P = parietal; Theta = 4–7 Hz.*

*p < .05; **p < .01.

TABLE S3 Correlations Between Resting-State Electroencephalographic Power and Attention-Deficit/Hyperactivity Disorder Behaviors

		Correlation With Visit 4 ADHD-RS Scores		
Electrode	**Frequency Band**	**Inattentive**	**Hyperactive/Impulsive**	**Total**
F4	Delta	−0.266	−0.319	−0.35*
F4	Theta	−0.252	−0.38*	−0.38*
F4	Beta 1	−0.254	−0.34*	−0.36*
F4	Beta 2	−0.261	−0.36*	−0.37*
F4	Gamma 1	−0.229	−0.31	−0.33
F4	Gamma 2	−0.218	−0.30	−0.31
Fz	Gamma 1	−0.183	−0.41*	−0.37*

Note: *ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale.*
*$p < .05$.

TABLE S4 Spontaneously Reported Adverse Events

	Participants Reporting			
	Active (n = 32)		Sham (n = 30)	
Adverse Event	n	%	n	%
Anxiety		1	3	
Bronchitis	1	3		
Headache	3	9	1	3
Itching	1	3		
Lightheaded	1	3		
Mouth pain		1	3	
Nausea	1	3		
Nightmares		1	3	
Poor appetite	1	3		
Rash	1	3		
Rhinitis	2	6	2	6
Skin whitening/discoloration	1	3	1	3
Stomachache	2	6	1	3
Tooth pain	1	3		
Upper respiratory infection	3	9	3	10
Vomiting	1	3		
Wrist sprain		1	3	

Note: *All adverse events were mild to moderate in clinical significance. There were no serious adverse events.*