DE NOVO CLASSIFICATION REQUEST FOR MONARCH eTNS SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Transcutaneous electrical nerve stimulator for Attention Deficit Hyperactivity Disorder. A transcutaneous electrical nerve stimulator for Attention Deficit Hyperactivity Disorder (ADHD) is a prescription device that stimulates transcutaneously or percutaneously through electrodes placed on the forehead.

NEW REGULATION NUMBER: 21 CFR 882.5898

CLASSIFICATION: Class II

PRODUCT CODE: QGL

BACKGROUND

DEVICE NAME: Monarch eTNS System

SUBMISSION NUMBER: DEN180041

DATE OF DE NOVO: July 31, 2018

CONTACT: NeuroSigma, Inc.
10960 Wilshire Boulevard
Suite 1910
Los Angeles, CA 90024

INDICATIONS FOR USE

The Monarch external Trigeminal Nerve Stimulation (eTNS) System is indicated for treatment of pediatric Attention Deficit Hyperactivity Disorder as a monotherapy in patients ages 7 through 12 years old who are not currently taking prescription ADHD medications. The device is used for patient treatment by prescription only and is intended to be used in the home under the supervision of a caregiver during periods of sleep.

LIMITATIONS

For prescription use only.

The device is contraindicated for use by patients with:

- Implanted cardiac and/or neurostimulation systems
- Implanted metallic or electronic device in their head

The device should not be applied on the neck or chest, and it should not be used in the presence of electric monitoring equipment (e.g. cardiac monitors), in the bath or shower, or while operating machinery.

The long-term effects of using the Monarch eTNS System are unknown.

The device should only be applied to healthy, clean, intact skin.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Monarch external Trigeminal Nerve Stimulation (eTNS) System is a non-invasive device that uses electrical signals to therapeutically stimulate the Trigeminal nerve. The primary components of the device are:

- The Monarch external pulse generator
- The Monarch NS-2 external (cutaneous) electrical patches, which are single use disposable patches worn on the forehead.

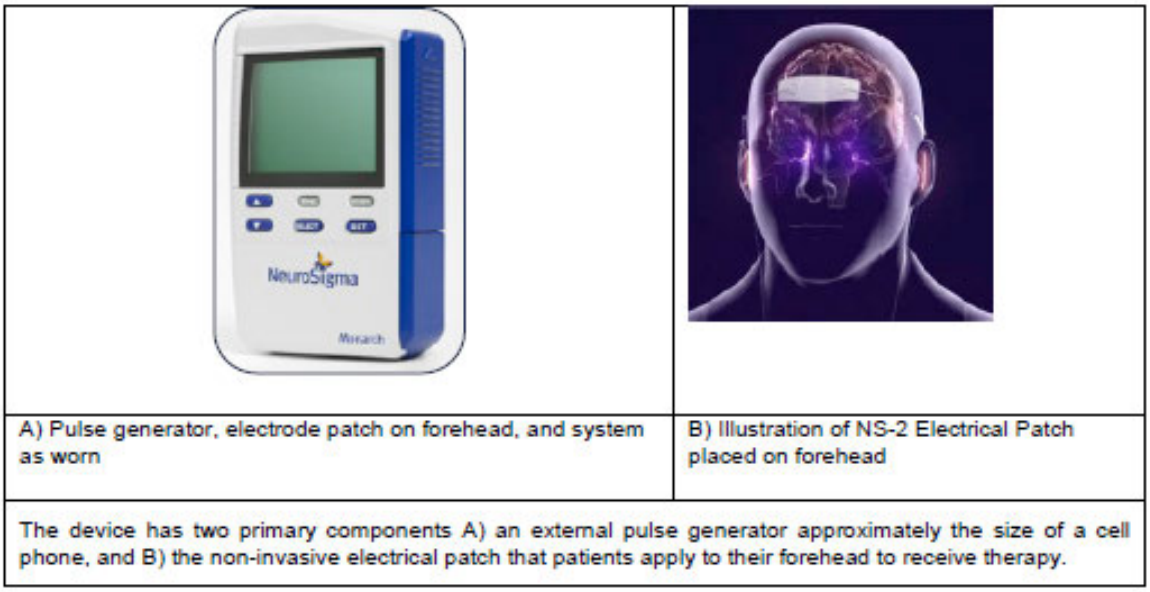


Figure 1: Monarch eTNS System

The Monarch External Pulse Generator

The Monarch pulse generator generates an electrical stimulus for delivery to the patient's forehead. It is housed in a sealed protective case and powered by a rechargeable lithium polymer battery. Accessories include two spare batteries and a battery charging station. The stimulation parameters generated by the Monarch eTNS System are summarized in Table 1. All parameters are fixed except for amplitude. Amplitude is controlled by the patient's caregiver. Under a

physician's supervision, the user can adjust the amplitude in 0.2mA increments, from 0 and 10 mA.

The Monarch NS-2 Electrical Patch

The Monarch eTNS patch attaches to the skin of the forehead by both hypoallergenic hydrogel and medical grade foam and adhesive and allows for bilateral stimulation of both the right and left supraorbital (SO) and supratrochlear (ST) branches of the trigeminal nerve (V1), located above the eyebrows in the forehead. The caretaker places the patch in the midline of the patient's forehead and applies the patch to the forehead directly above the eyebrows.

The gel, foam, and adhesive have undergone skin sensitization and histocompatibility studies in animals according to ISO 10993-1: Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing. The electrical patch is connected to the pulse generator via a lead wire.

Stimulation Parameters:

Electrical Stimulation parameters generated by the Monarch eTNS System are summarized in the table below:

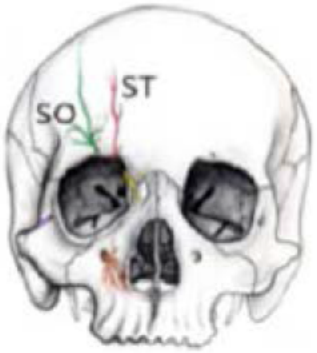
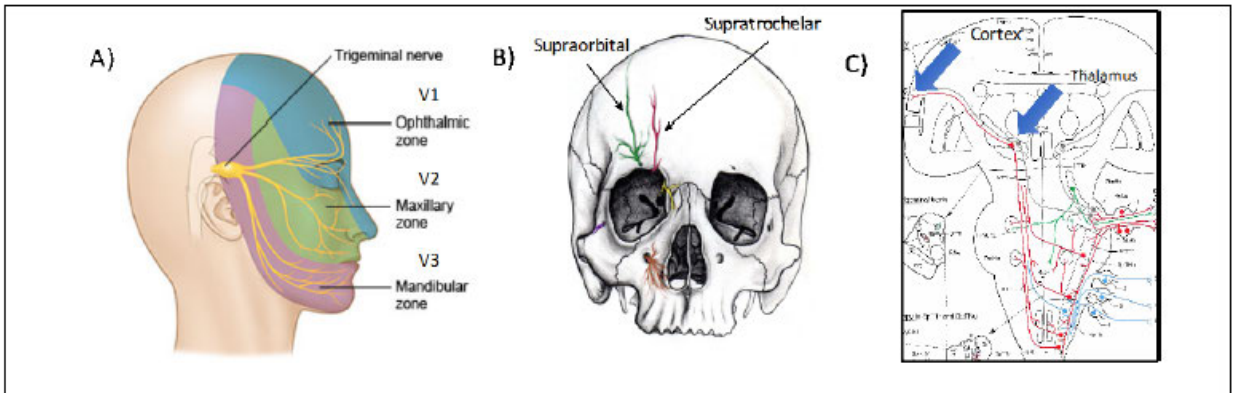
Parameter	Outcome
Waveform	Symmetrical Square Wave
Frequency of Stimulation	120 Hz
Pulse Width	250 µSec
Duration between pulses	8 mSec
Maximum stimulus intensity	10 mA, under patient control
Maximum Output Voltage	5.36V
Hours of use	7 – 9 hours, while asleep, as prescribed by treating physician
Cycling	30 Sec ON: 1 Sec Ramp Down: 30 Sec OFF: 1 Sec Ramp Up
Net Charge per pulse	2.5 µC per pulse
Maximum current density	1.4 $mA.cm^2$
Maximum average power density	7.5 mW/cm^2
Maximum average current	10 mA
Maximum Charge Density	0.35 $\mu C/cm^2$
Maximum Average power density	7.5 mW/cm^2
Stimulating Surface Area of NS-2 Patch	7.1 cm^2 per electrode
Anatomical Target	Supraorbital (SO) and Supratrochlear (ST) nerves of the V1 division of the Trigeminal Nerve 

Table 1: Stimulation Parameters

Principle of Operation:

The Monarch eTNS System treatment protocol is administered each night while the patient is sleeping, for 7 – 9 hours. The device is designed to provide non-invasive electrical stimulation of the trigeminal nerve. The trigeminal nerve is the largest cranial nerve and has three major sensory divisions of the face (V_1, V_2, V_3), all of which are bilateral. The trigeminal nerve provides a direct connection to multiple brain structures implicated in ADHD and other neurologic and neuopsychiatric disorders.[1234]



A) The Trigeminal nerve provides sensation to the face via three divisions (V1, V2, V3). eTNS stimulates the V1 division. B) The Supraorbital (SO) and Supratrochlear (ST) nerves are terminal branches of the V1 division. These four nerves, two on each side of the forehead, are the stimulation targets for eTNS. C) Path of the Trigeminal as it enters the brainstem at the level of the Pons then makes connections in the medulla and midbrain before making connections in the thalamus and cortex.

Figure 2: Anatomy of the Trigeminal Nerve

SUMMARY OF NONCLINICAL AND BENCH STUDIES

Biocompatibility, electrical safety, electromagnetic compatibility, battery safety, waveform verification, shelf life and software testing was required for the Monarch eTNS System.

BIOCOMPATIBILITY/MATERIALS

Patient contacting materials of the Monarch eTNS System are limited to the materials of the NS-2 electrode patch.

Patient Contacting Device Component	Nature of Tissue Contact	Duration of Tissue Contact
NS-2 Electrical Patch / Hydrogel (Multistick MG-1500 AG600)	Skin Contact	7 – 9 hours; During Sleep

[1] Nolte J. The Human Brain. An introduction to its functional anatomy. Mosby. 6th edition. 2009.

[2] Caous CA, de Sousa Buck H, Lindsey CJ. Neuronal connections of the paratrigeminal nucleus. AutonNeurosci 2001; 94:14-24.

[3] Grzanna R, Chee WK, Akeyson EW. Noradrenergic projections to brainstem nuclei: evidence for differential projections from noradrenergic subgroups. J Comp Neurol 1987; 263:76-91.

[4] Krout KE, Belzer RE, Loewy AD. Brainstem projections to midline and intra-laminar thalamic nuclei of the rat. J Comp Neurol 2002; 448:53-101.

NS-2 Electrical Patch / adhesive foam (MTDID 22459 A3)	Skin Contact	7 – 9 hours; During Sleep

Table 2: List of Patient-Contacting Materials

The electrode has limited duration (<24 hours) with intact skin. Therefore, per the FDA guidance "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"", and ISO 10993-1: Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing, cytotoxicity, sensitization, and irritation testing were performed for the electrode. The following table summarizes the tests performed and the results:

Test Article	Test/Stand	Method	Results
Hydrogel (Multistick MG-1500 AG600)	Intracutaneous Reactivity/ISO 10993-10	Intracutaneous toxicity in rabbits	PASS
	Sensitization/ISO 10993-10	Guinea Pig closed path sensitization	PASS
	Cytotoxicity/ISO 10993-5	MEM Elusion	PASS
Medical Grade adhesive foam (MTDID 22459 A3)	Irritation/ISO 10993-10	Intracutaneous toxicity in rabbits	PASS
	Sensitization/ISO 10993-10	Guinea Pig maximization sensitization	PASS
	Cytotoxicity/ISO 10993-5	MEM Elusion and Agarose Overlay Method	PASS

Table 3: Summary of Biocompatibility Testing Results

SHELF LIFE/STERILITY

The Monarch eTNS device and its accessories are not sterile. Cleaning and maintenance instructions for the system are included within the labeling.

The Shelf Life of the Monarch NS-2 electrodes is 3 years, as determined by accelerated and real-time age testing.

ELECTROMAGNETIC COMPATIBILITY (EMC) AND ELECTRICAL SAFETY

The Monarch eTNS system was tested to demonstrate conformance to the following electromagnetic compatibility, electrical, mechanical, and thermal safety standards:

- Electromagnetic Compatibility
    - IEC 60601-1-2 - Medical Electrical Equipment; Part 1-2: General Requirements for Safety – Section 2: Collateral Standard: Electromagnetic Compatibility - Requirements and Tests.

- Electrical, Mechanical, and Thermal Safety

    - IEC 60601-1:2012 - Medical Electrical Equipment; Part 1: General Requirements for Basic Safety and Essential Performance.

    - IEC 60601-1-11:2015 – Medical Electrical Equipment Part 1-11: Collateral Standard Requirements for Medical Electrical Equipment and medical electrical systems used in home healthcare environment.

    - IEC 60601-2-10 - Medical Electrical Equipment; Part 2-10: Particular Requirements for the Safety of Nerve and Muscle Stimulators (2016).

- Battery Safety

    - IEC 62133:2012 - Secondary cells and batteries containing alkaline or other non-acid electrolytes - Safety requirements for portable sealed secondary lithium cells, and for batteries made from them, for use in portable applications - Part 2: Lithium systems

SOFTWARE

Proprietary Software of the Monarch eTNS system was reviewed according to FDA Guidance document, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," issued May 11, 2005. The software was found to have a MODERATE level of concern. FDA review of the software documentation provided in support of the Monarch eTNS System was found to be acceptable.

PERFORMANCE TESTING – BENCH

The following tests were conducted to demonstrate device reliability:

- Battery Performance Testing: The device operated for the intended duration of use to demonstrate that the battery could power the system for this period of time.
- Stimulation Output Verification Testing: Output waveforms were captured using an oscilloscope to demonstrate that the device can produce its intended stimulation parameters.
- Electrode Testing: Electrical performance, adhesive integrity, and shelf life testing of the electrode was tested to ensure that its electrical performance and adhesive properties met specifications for the duration of its shelf life.

Performance Testing (Bench) was found to be acceptable

SUMMARY OF CLINICAL INFORMATION

Two clinical trials, eTNS-ADHD01 (Study 1) and eTNS-ADHD02 (Study 2), were conducted and each trial is summarized below.

A. Study 1 – eTNS-ADHD01 (NCT01388530)

eTNS-ADHD01 was an open label trial reporting the outcomes of 24 children ages 7 through 14 with moderate to severe ADHD. Moderate to severe ADHD was defined as having a minimum score of 12 on both the inattentive and hyperactive and impulse subscales of the baseline ADHD Rating Scale (ADHD-RS) and a Clinical Global Impression-Severity (CGI-S) score at baseline of greater than 4. Patients underwent 8 weeks of nightly treatments with eTNS as a monotherapy. The primary effectiveness endpoint in this study was the ADHD-IV Rating Scale (ADHD-RS). Secondary and Exploratory endpoints included the following:

1. CGI-Improvement Scale
2. Conners Parent and Teachers Indexes
3. Children Depression Inventory (CDI)
4. Beck Depression Inventory (BDI)
5. Manifest Anxiety Scale for Children (MASC)
6. Brief Family Assessment Measure III (Brief FAM-III)
7. Behavior Rating Inventory of Executive Functioning (BRIEF)
8. Cognitive tests (ANT, SDRT, Go/No Go)
9. Children's Sleep Habits Questionnaire

eTNS-ADHD01 was designed to obtain preliminary data on the acceptability, tolerability, and potential effectiveness of eTNS as an ADHD treatment. This 8-week trial duration was based on clinical trials of pharmaceutical treatments for ADHD as well as other clinical trials of eTNS for different neuropsychiatric indications that found significant effects after 8 weeks.

1. Study 1

Patients in eTNS-ADHD01 used the Neurosigma NS-2 disposable patch and the EMS 7500 Transcutaneous Electrical Nerve Stimulator (TENS) device. The EMS 7500 used the same electrical output parameters as the Monarch eTNS System. Each NS-2 electrical patch was used for a single, nightly treatment session and disposed of in the morning.

2. Background and Trial Design

ADHD diagnosis was based on the DSM-IV criteria for ADHD. Once inclusion/exclusion criteria were met, participants had a pre-treatment visit to assess baseline ADHD symptom severity on the ADHD-RS scale and several measures of cognition. Following the baseline visit, subjects initiated nightly therapy with eTNS. Parents/Caregivers were instructed to start treatment shortly before sleep. The disposable patch was applied to the center of the subject's forehead, just above the eyebrows, and connected to the external stimulator via the lead wire. Parents/Caregivers were instructed to increase the current to the point of perceptibility, and to keep it at that level throughout the night. Upon waking, subjects removed the patch and went about their normal daily activities. Patients were required not to use any ADHD medications at baseline and throughout the study.

After initiating therapy with eTNS, participants returned for 8 weekly clinic visits, which included repeated assessment of behavioral response, tolerability, and compliance. Treatment compliance was measured daily with a parent completed compliance diary and weekly by clinical interviews conducted at study visits. Visits at weeks 4 and 8 also

included repeated measurements of cognitive outcomes. Additionally, teacher rating of ADHD symptoms were collected when available at baseline, week 4 and week 8. The pre-specified primary outcome measure was the investigator completed ADHD-RS.

3. Statistical Analysis

Participation rates and treatment compliance were determined based on all participants deemed eligible at screening. The safety population included all participants with at least one night's exposure to eTNS. The treatment population included all participants with outcome data at Week 4 which was the first post-baseline point at which primary behavioral and cognitive outcomes were obtained.

4. Results

A total of 29 individuals were screened for participation. Of those screened 25 met inclusion/exclusion criteria. Twenty-four subjects initiated eTNS treatment as there was an early termination for 1 subject for which no other information was provided. Two participants dropped out prior to visit 4, and one dropped out after visit 4. According to daily treatment diaries from subjects that completed the trial, nightly treatment compliance was 100%. The Safety Analysis was based on the 24 participants with any exposure to eTNS. Treatment Analysis was based on the 22 participants with baseline and visit 4 data. Participant demographics is summarized in the below table:

Sample Size (N)	24	
Sex	92% male, 8% female	
Age: Mean (SD), Range	10.3 (2.1)	7-14 years
Full Scale IQ: Mean (SD), Range	100.7 (12.7)	75-127
Race		
White	75 %	
African American	13 %	
Asian	13 %	
Ethnicity		
Non-Hispanic	54 %	
Hispanic	46 %	
ADHD Subtype		
Inattentive	8%	
Hyperactive/Impulsive	4%	
Combined	88%	
Comorbidity (%)		
Oppositional Defiant Disorder	46%	

*Safety population based on all participants exposed to TNS

Table 4: eTNS-ADHD01 Participant Characteristics

88% met criteria for the combined subtype of ADHD. 46% had comorbid oppositional defiant disorder (ODD).

a) Safety

A total of 13 adverse events (AE) were reported during the 8-week pilot trial. Of these, 2 events (eye twitching and headache) were deemed as potentially related to the evaluated treatment. The eye twitch resolved with alternative placement of forehead electrodes. Two patient reported headache, which were resolved without additional intervention. Table 5 presents adverse events reported during the study and Table 6 summarizes side effects which were rated on at least one visit as being "moderate" or "severe".

Event	Number of Incidents	Related or Possibly Related*	Unrelated*	% Participants Reporting
Asthma	1	0	1	4.2%
Eye Twitch	1	1	0	4.2%
Gagging	1	0	1	4.2%
Headache	4	2	2	16.7%
Inguinal Hernia	1	0	1	4.2%
Nasal Congestion	1	0	1	4.2%
Sore Throat	2	0	2	8.3%
Swallowed Tack	1	0	1	4.2%
Tingles in Head	1	0	1	4.2%

*Determination made by study investigators

Table 5: Adverse Events (N=24)

Side Effect	% Participants Reporting	Number of Incidents
Trouble concentrating **	92	22
Trouble sitting still **	71	17
Poor concentration **	71	17
Feeling nervous or hyper	58	14
Poor memory **	46	11
Irritable	42	10
Trouble Sleeping	29	7
Stuffy nose	24	6
Nightmares or other sleeping disturbances	21	5
Feeling drowsy or sleepy	21	5
Weakness or fatigue	21	5
Headache	13	3
Diminished mental acuity/sharpness	13	3
Apathy/emotional indifference	13	3
Feeling strange or unreal	8	2
Drooling or increased salivation	8	2
Muscle twitching or movements	8	2

Slurred speech	8	2
Stomach or abdominal discomfort	8	2
Excess sweating	8	2
Weight gain	8	2
Difficulty finding words	8	2
Blurred vision	4	1
Dry mouth	4	1
Rapid heartbeat	4	1
Hyperventilation	4	1
Difficulty starting urination	4	1
Frequent need to urinate	4	1
Appetite decreased	4	1
Appetite increased	4	1
Skin rash or allergy	4	1
Hair thinning/loss	4	1

Table 6: Moderate and Severe Side Effects Based on SAFTEE Rating Scale (N = 24)

b) Effectiveness

Results are summarized in Table 6 and Figure 5. The change in ADHD-RS results are presented for baseline, week 4, and week 8. The mean score on ADHD-RS was 32.6 at baseline versus 18.2 at week 4 and 17.3 at week 8.

Measure	Study Week Least Square Means					
	Baseline	Week 4	Week 8	F	d/f	p value
ADHD-RS-Total	32.6	18.2	17.3	42.45	2/340	<.0001
ADHD-RS-Inattentive Subscale	17.8	10.9	10.1	30.25	2/40	<.0001
ADHD-RS-Hyper/Imp Subscale	14.8	7.3	7.3	30.31	2/40	<.0001

Table 7: ADHD-IV RS Scale Results

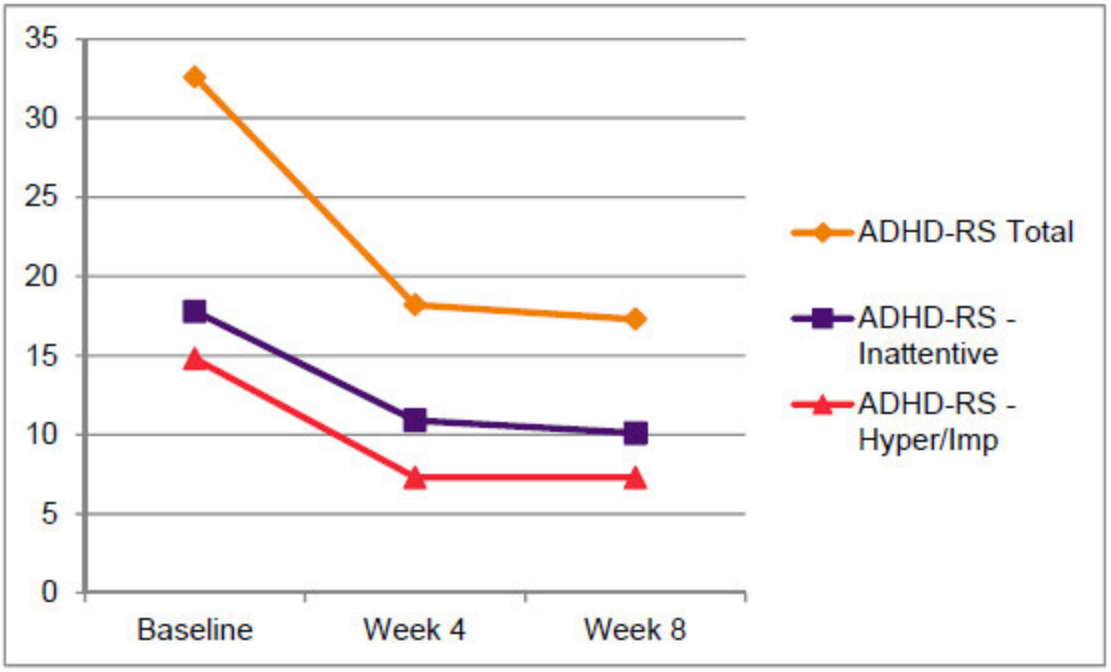


Figure 3: ADHD-RS Results

c) Feasibility Study Results

No serious adverse events were reported, and the treatment was well tolerated in this feasibility study. Preliminary mean scores improved from 32.6 points at baseline to 18.2 points at Week 4 and 17.3 points at Week 8.

d) Study 1 Limitations

Additional factors to be considered in determining a reasonable assurance of safety and effectiveness includes the small sample size, open label studies may cause an overestimation of the treatment effect due to investigator and subject ratings. Also, open label studies do not assess the magnitude of the placebo response, the effect of changes in medications or the contribution of other treatments.

B. Study 2 - eTNS-ADHD02 (NCT02155608)

1. Background and Trial Design

eTNS-ADHD02 was a double blind, randomized, sham controlled trial of the external trigeminal nerve stimulation (eTNS) for the treatment of pediatric ADHD. The purpose of this study was to evaluate the safety and effectiveness findings of eTNS-ADHD01. The primary endpoint was the ADHD-IV RS. Secondary endpoints included:

- CGI-I

The primary endpoint was measured at 4 weeks based on results from eTNS-ADHD01. Patients in this trial were not permitted to take medications for ADHD to ensure the

effectiveness of the device could be assessed without confounding variation due to medication. Prior to device therapy, patients were requested to stay off medication for at least a week.

Subjects were randomized 1:1 to either the active treatment or sham stimulation groups. Subjects randomized to the sham group received a Monarch eTNS system identical in appearance and graphical user interface to the active device. However, stimulation was routed through an internal resistor instead of the adhesive electrical patch. This ensured that the rechargeable battery still drained appropriately and required the subject to recharge it after each nightly therapy session to maintain the study blind. To further protect study blinding, subjects were counseled during enrollment that stimulation may not be perceptible, and all patients received an "early impression questionnaire" at their Week 1 visit to determine if there were statistically significant differences in impressions of treatment.

Each night parents/caregivers were instructed to apply a patch to their forehead, turn on the device and increase stimulation to the maximum tolerable level. Once this maximum level was reached, patients were instructed to reduce it by 0.1 mA. Compliance was assessed during the weekly visit by reviewing the subject diaries.

Subjects were instructed to begin their eTNS therapy each night before sleep. Initiation of therapy consisted of applying the NS-2 electrical patch to the midline of the subject's forehead just above the eyebrows, subsequently followed by setting the amplitude to a comfortable level. Stimulation was then applied throughout the night while the subject was sleeping.

2. Enrollment

79 subjects were screened for trial participation. Of these, 13 failed to meet trial inclusion criteria, 2 met exclusion criteria, and 2 were lost to follow up prior to the baseline visit. 62 subjects were enrolled and randomized (32 to the active group and 30 to the sham group). Of these, 3 terminated the study early, but did participate in at least one efficacy assessment. 59 subjects completed the 4week double blind treatment period (31 in the active group and 28 in the sham group).

3. Accountability

Of the 62 subjects randomized in the study, 94% of active subjects and 83% of sham subjects reported complete compliance data for each endpoint at the 4 weeks follow up visit. The following table presents patient compliance with the study.

4. Demographics

A summary of subject demographics is presented in table 9. Sixty-three percent (63%) of subjects had the combined subtype of ADHD, 34% had the inattentive subtype, and 3% had the hyperactive/impulsive subtype. In addition, subject demographics show that the population evaluated was diverse and representative of the intended US treatment population.

	Total Sample (N=62)		Active Group (n=32)		Sham Group (n=30)		P Value
Age, Mean (SD) Years	10.4	(1.4)	10.3	(1.4)	10.5	(1.4)	0.49
[Range]	[8.1-13.0]		[8.1-12.9]		[8.2-13.0]		
Height, Mean (SD) cm	141.8	(9.2)	142.7	(10.2)	140.0	(8.1)	0.44
[Range]	[126.0-160.3]		[126.0-160.3]		[126.8-157.2]		
Weight, Mean (SD) kg	37.3	(11.1)	38.4	(12.4)	36.0	(9.4)	0.41
[Range]	[23.3-77.0]		[23.3-77.0]		[23.5-67.2]		
Full Scale IQ, Mean (SD)	108.9	(13.2)	110.4	(12.3)	107.3	(14.2)	0.35
[Range]	[81.0-144.0]		[87.0-134.0]		[81.0-144.0]		
Sex, n (%)							
Male	40	(65)	20	(63)	21	(70)	0.38
Female	22	(35)	13	(40)	9	(3)	
Race, n (%)							
White	40	(65)	20	(63)	20	(67)	0.21
Black	4	(6)	4	(13)	0		
Asian	10	(16)	5	(16)	5	(17)	
Mixed/Other	8	(13)	3	(9)	5	(17)	
Ethnicity, n (%)							
Non-Hispanic	52	(84)	27	(84)	25	(83)	0.91
Hispanic	10	(16)	5	(16)	5	(17)	
ADHD Subtype, n (%)							
Combined	39	(63)	22	(69)	17	(57)	0.60
Inattentive	21	(34)	9	(28)	12	(40)	
Hyperactive/Impulsive	2	(3)	1	(3)	1	(3)	
Comorbid Disorders, n (%)							
Oppositional Defiant	20	(32)	11	(34)	9	(30)	0.71
Disruptive Mood Dysregulation	17	(27)	10	(31)	7	(23)	0.49
Social Phobia	10	(16)	7	(21)	3	(10)	0.20
Separation Anxiety	2	(3)	1	(3)	1	(3)	0.96
Generalized Anxiety	10	(16)	6	(19)	4	(13)	0.96
Any Anxiety	18	(29)	11	(3)	7	(23)	0.34
Enuresis	6	(12)	5	(16)	1	(3)	0.10
Encopresis	2	(3)	0		2	(7)	0.14
Tourette's Syndrome	2	(3)	2	(6)	0		0.16
Motor Tic	1	(2)	0		1	(3)	0.30

Table 8: Subject Demographics

5. Results

a) Safety

There were no significant differences in vital signs between baseline and week 4 or between active and sham treatment groups. eTNS was well tolerated in all 62 subjects. Of the reported adverse events, all were mild to moderate in severity.

There were no serious adverse events (SAEs) associated with the use of the device.

Event	% of Participants Reporting Event During Study	
	Active (n=32)	Sham (n=30)
Hyperactive	41	63
Drowsy	22	13
Increased appetite	19	7
Trouble sleeping	19	17
Stuffy nose	16	20
Clenching teeth	13	7
Fatigue	13	3
Headache	13	3
Constipation	9	7
Upper Respiratory Infection	9	10
Apathy	6	7
Frequent urination	6	0
Nightmares	6	3
Rhinitis	6	6
Skin rash	6	0
Stomachache	6	3
Bronchitis	3	0
Decreased appetite	3	3
Frequent sweating	3	3
Itching	3	0
Lightheaded	3	0
Muscle cramps	3	3
Nausea	3	0
Out of breath	3	3
Rapid heartbeat	3	0
Skin whitening/discoloration	3	3
Tingling	3	0
Tooth pain	3	0
Vomiting	3	0
Anxiety	0	3
Difficulty finding words	0	7
Feeling strange	0	7
Mouth pain	0	3
Muscle twitch	0	7
Slurred speech	0	3
Tremor	0	3
Wrist sprain	0	3

Table 9: Safety Results - Adverse Events

b) Efficacy

(1) Early Impressions Questionnaire (Blinding Assessment)

	Odds Ratio (Active vs. Sham)	95% Confidence Interval	Wald Chi-Square df	P Value
At this point, how successfully do you think your current TNS treatment will be in reducing your child's ADHD symptoms?	.93	.76 – 1.15	$.45_1$	.50
At this point, how much do you really feel that TNS treatment will help reduce your child's ADHD symptoms?	.90	.70 – 1.14	$.82_1$	.37

Table 10: Early Impression Questionnaire Results

All patients were assessed for blinding at the 1 week follow up visit using an Early Impression Questionnaire. Results demonstrated that there was no significant difference in caregiver expectations between active and sham groups regarding expectations of a positive treatment effect.

(2) Primary Efficacy Endpoint

The primary endpoint was the ADHD-IV Rating Scale. Upon completion of the 4-week blinded treatment protocol, the average ADHD-RS score in the active group decreased from 34.1 points at baseline to 23.4 points. Within the sham group, a decrease from 33.7 points at baseline to 27.5 points was recorded. As seen in Figure 5 below, both groups saw a decrease in ADHD-RS total score over Week 1 of the study. This was followed by ongoing improvement in the active group as compared to flattening of the curve in the sham group.

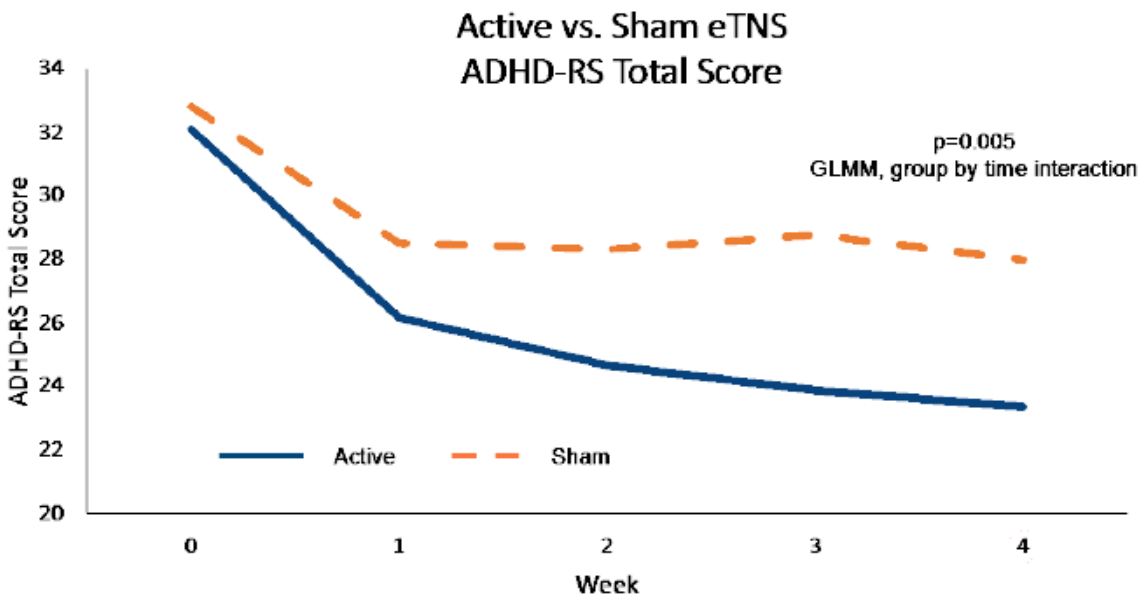


Figure 4: Mean ADHD-RS Total Score by Time Point by Group

Time Point	Active (N = 31)		Sham (N = 28)	
	Mean	SD	Mean	SD
Baseline (Visit 0)	34.06	6.64	33.7	7.21
Week 1 (Visit 1)	26.16	7.67	28.53	8.78
Week 2 (Visit 2)	24.74	9.01	27.54	7.84
Week 3 (Visit 3)	23.59	7.24	28.13	8.96
Week 4 (Visit 4)	23.39	7.88	27.5	8.08

Table 11: Mean ADHD-RS Total Score by Time Point and Group

Treatment effect size was determined using the Cohen's d test and demonstrated a medium effect in ADHD-RS Total scores.

.

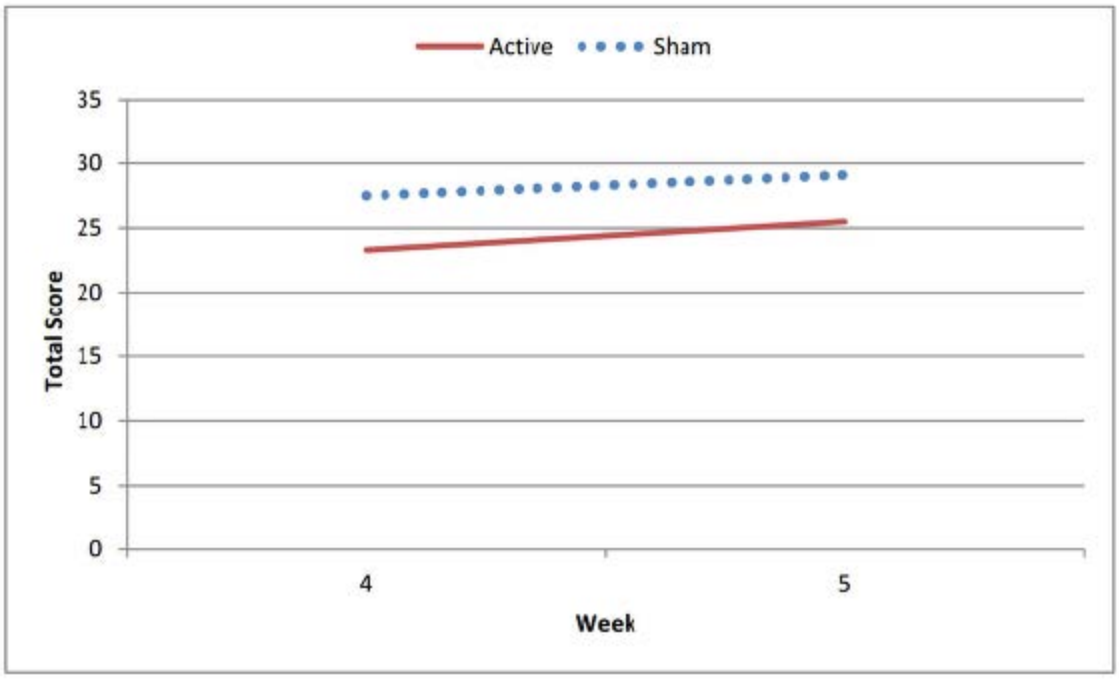


Figure 5: ADHD-RS Total Scores over Blinded Discontinuation Week - Active Vs. Sham TNS

In addition, long term data was collected for a subset of patients with clinically meaningful improvement on active eTNS treatment during Study 2. This was defined as those whose had a CGI-I score of ≤ 2. These patients were offered the opportunity to continue using the device for an additional 12 months in an open label extension phase. This opportunity was open to active group subjects following their initial 4 weeks of blinded treatment and to those of the sham group who chose to enter the cross over phase.

Time Point	Number of Subjects	
	Started in Active Group	Started in Sham Group
3 Months	10	8
6 Months	5	3
9 Months	4	2
12 Months	2	1

Table 12: Long Term Data Accountability

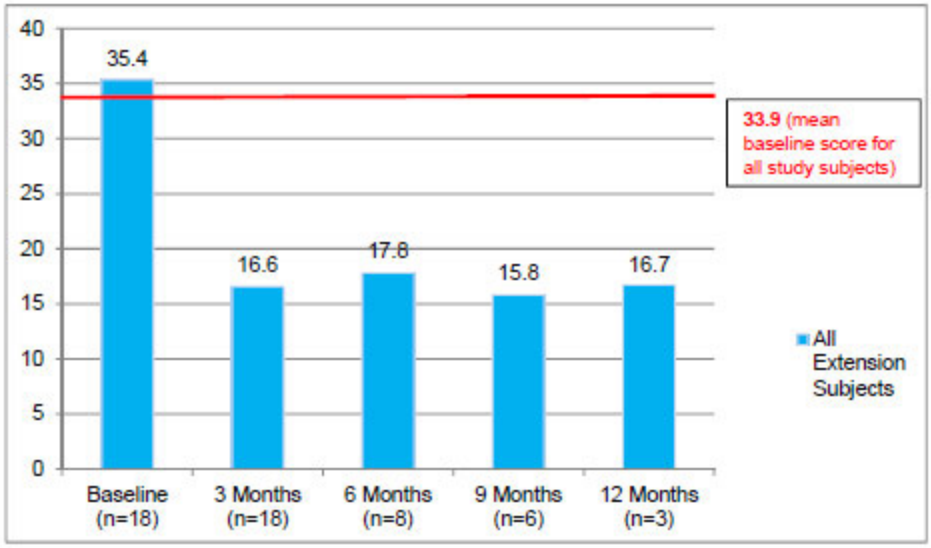


Figure 6: Mean ADHD-RS Total Score by Time Point in Open Label Extension

c) Secondary Efficacy Endpoints

Data from the CGI-I scale demonstrated a statistically significant result from eTNS treatment. After 4 weeks of study treatment, 52% of subjects in the active group improved by one or more points on the CGI-I scale versus 14% of subjects in the sham group. Additionally, data from weeks 1 – 4 of treatment show a steadily increasing improvement among subjects in the active group versus no significant change among subjects in the sham group.

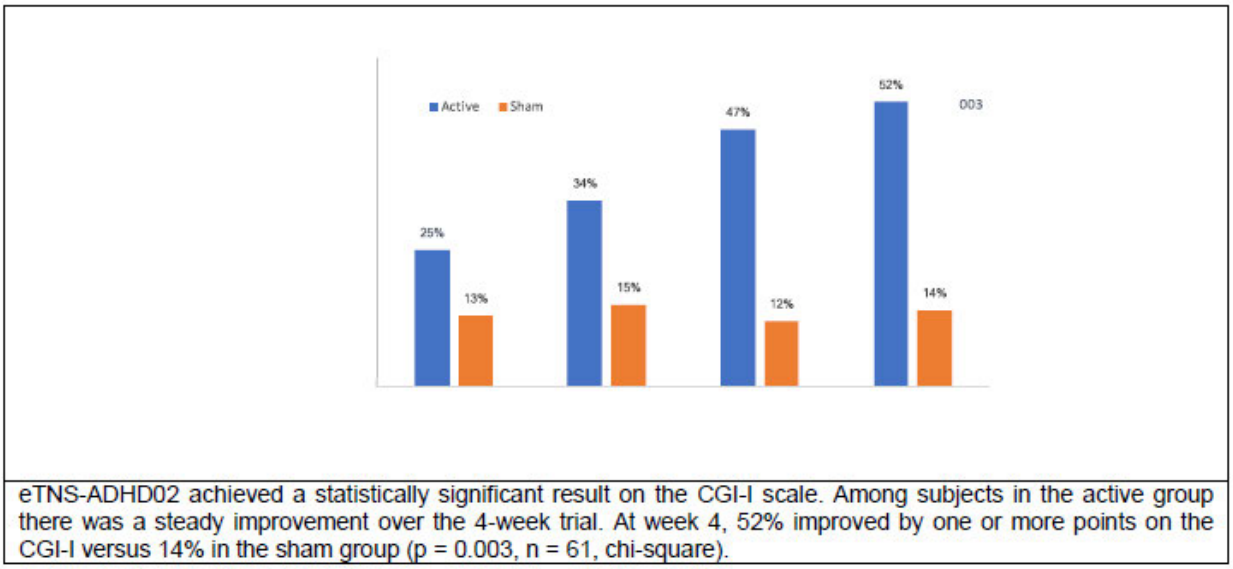


Figure 7: Percent of Group Reporting Improvement on CGI-I Scale

	Active		Sham			
Week	Not Improved n (%)	Improved n (%)	Not Improved n (%)	Improved n (%)	X^2_{df}	P Value
1	24 (75)	8 (25)	26 (87)	4 (13)	1.35_1	0.25
2	19 (61)	12 (34)	22 (85)	4 (15)	3.81_1	0.05
3	16 (53)	14 (47)	22 (88)	3 (12)	7.67_1	0.006
4	15 (48)	16 (52)	24 (86)	4 (14)	9.12_1	0.003

* improved = CGI-I ≤2 ; not improved = CGI-I >2.

Table 13: CGI-I by Study Week

d) Study 2 Limitations

Additional factors to be considered in determining a reasonable assurance of safety and effectiveness includes the small sample size and the potential for unblinding subjects in the sham arm which may have resulted in patient bias and the outcomes reported for treatment groups. In addition, the design of Study 2 did not allow an assessment of the placebo response.

LABELING

The Monarch eTNS System Instructions for Use are consistent with the clinical data and cover all the hazards and other clinically relevant information that may impact use of the device. The labeling is sufficient and satisfies the requirements of 21 CFR § 801.109 Prescription devices. The Monarch eTNS System is contraindicated for the following uses:

The device is contraindicated for use by patients with:

- Implanted cardiac and/or neurostimulation systems
- Implanted metallic or electronic device in their head

The following warnings and precautions are included within device labeling:

- The device should not be applied on the neck or chest, and it should not be used in the presence of electric monitoring equipment (e.g. cardiac monitors), in the bath or shower, or while operating machinery.
- The long-term effects of using the Monarch eTNS System are unknown.
- The device should be used only as direct and be applied to healthy, clean, intact skin.

The labeling also includes:

- Information on how the device operates and the typical sensations experienced during treatment;
- A detailed summary of the device technical parameters;
- A shelf life for the electrodes;
- Information in the Instructions for Use regarding how to place the device on the patient; and
- Cleaning instructions for the device.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of a transcutaneous nerve stimulator for Attention Deficit Hyperactivity Disorder (ADHD) and the measures necessary to mitigate these risks.

Identified Risk	Mitigation Measures
Adverse tissue reaction	Biocompatibility evaluation
Injury or discomfort from electrical stimulation, including burns and nerve damage	Electromagnetic compatibility testing Electrical, mechanical, and thermal safety testing Non-clinical performance testing Software verification, validation, and hazard analysis Shelf life testing Labeling
Misuse that may result in device failure, user discomfort, or injury	Labeling
Skin irritation or infection from use on broken skin	Labeling

Table 14: Identified Risks to Health and Mitigation Measures

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the transcutaneous electrical nerve stimulator for Attention Deficit Hyperactivity Disorder (ADHD) is subject to the following special controls:

1. The patient-contacting components of the device must be demonstrated to be biocompatible.

2. Performance testing must demonstrate the electromagnetic compatibility and electrical, mechanical, and thermal safety of the device.

3. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following must be performed:
    a. Electrical performance testing must validate electrical output and duration of stimulation;
    b. Battery performance testing must be performed; and
    c. Adhesive integrity testing of the electrodes must be conducted.

4. The technical parameters of the device including waveform, maximum output current and voltage, pulse duration, frequency, net charge per pulse, maximum current density, maximum average current, and maximum average power density must be fully characterized.

5. Software verification, validation, and hazard analysis must be performed.

6. Shelf life testing of the electrodes must be performed to demonstrate continued package integrity and component functionality over the labeled shelf life.

7. Labeling must include the following:
    a. A contraindication for patients with an implanted metallic or electronic device in the head, a cardiac pacemaker, or an implanted or wearable defibrillator;
    b. A warning that the device is only for use on clean, intact skin;
    c. Information on how the device operates and the typical sensations experienced during treatment;
    d. A detailed summary of the device technical parameters;
    e. A shelf life for the electrodes;
    f. Instructions for use, including placement of the device on the patient; and
    g. Cleaning instructions.

BENEFIT/RISK DETERMINATION

The risks of the Monarch eTNS Therapy System are based on data collected from two studies. No serious adverse events were reported in either study and all adverse events were minor with reversible effects. In Study 2, differences in side effects seen between patients in the active compared to the sham group included nightmares, headache, frequent urination, increased appetite, skin rash, and teeth clenching. However, none of the patients were reported to discontinue treatment based on headaches or any of the other adverse effects.

The probable benefits of the device are based on data collected from the randomized sham-controlled trial that demonstrated a clinically meaningful and statistically significant improvement in the ADHD-RS total score over the 4-week treatment period. Data from both Study 1 and long term follow up portion of Study 2 indicates that there may be continued benefit beyond 4 weeks. However, this benefit was not studied in a controlled manner.

Additional factors considered in determining probable risks and benefits for the Monarch eTNS Therapy System include:

1. Medications approved for ADHD provide a similar benefit but may have problematic side effects.
2. Long term effects of eTNS therapy (beyond 4 weeks) has not been evaluated.
3. Blinding was not assessed after the week 1 assessment in the one blinded trial.

Based on the results of the feasibility study and the randomized, sham controlled, clinical trial to support the use of a transcutaneous nerve stimulator for the treatment of ADHD in a pediatric population (ages 7 – 12, and assessment of the adverse event reported, we conclude that the benefits outweigh the probable risks.

Patient Perspectives

Patient and caregiver self-reported measures along with patient diaries were used to collect information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that for the previously stated indications for use, the probable benefits outweigh the probable risks for the Monarch eTNS System. The device provides benefits and the risks can be mitigated using general controls and the identified special controls.

CONCLUSION

The De Novo request for the Monarch eTNS Therapy System is granted and the device is classified under the following:

Product Code: QGL
Device Type: Transcutaneous electrical nerve stimulator for Attention Deficit Hyperactive Disorder
Class: II
Regulation: 21 CFR 882.5898

REFERENCES

1. Nolte J. The Human Brain. An introduction to its functional anatomy. Mosby. 6th edition. 2009.
2. Caous CA, de Sousa Buck H, Lindsey CJ. Neuronal connections of the paratrigeminal nucleus. AutonNeurosci 2001; 94:14-24.
3. Grzanna R, Chee WK, Akeyson EW. Noradrenergic projections to brainstem nuclei: evidence for differential projections from noradrenergic subgroups. J Comp Neurol 1987; 263:76-91.
4. Krout KE, Belzer RE, Loewy AD. Brainstem projections to midline and intra-laminar thalamic nuclei of the rat. J Comp Neurol 2002; 448:53-101.
5. McGough et al, An Eight-week, Open-trial, Pilot Feasibility Study of Trigeminal Nerve Stimulation in Youth With Attention-deficit/Hyperactivity Disorder. **Brain Stimulation** 8 (2015) 299-304.
6. McGough JJ, Sturm A, Cowen J, Tung K, Salgari GC, Leuchter AF, Cook IA, Sugar CA, Loo SK. Double-Blind, Sham-Controlled, Pilot Study of Trigeminal Nerve Stimulation for Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry. 2019 Apr;58(4):403-411.e3. doi: 10.1016/j.jaac.2018.11.013. Epub 2019 Jan 28.