March 27, 2024

Neurovalens Ltd.
Jason Mckeown, MD
CEO
8 Carmagrim Road
Ballymena, County Antrim BT44 8BP
United Kingdom

Re: K232253
Trade/Device Name: Modius Stress
Regulation Number: 21 CFR 882.5800
Regulation Name: Cranial electrotherapy stimulator
Regulatory Class: Class II
Product Code: QJQ
Dated: February 26, 2024
Received: February 26, 2024

Dear Dr. McKeown:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic.

See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Pamela D. Scott -S

Pamela Scott, MS
Assistant Director
DHT5B: Division of Neuromodulation
and Rehabilitation Devices
OHT5: Office of Neurological
and Physical Medicine Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K232253

Device Name

Modius Stress

Indications for Use *(Describe)*

Modius Stress is a non-invasive, home-use neurostimulation device that is indicated to treat the symptoms of Generalized Anxiety Disorder in adults aged 22 and older, when used for approximately 4 weeks. Durability of effect after 4 weeks has not been established.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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Modius Stress K232253
Summary

This 510(k) Summary is submitted in accordance with 21 CFR Part 807, Section 807.92.

I. Submitter

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Contact person/ official correspondence:
Dr Jason McKeown
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II. Device

Name of Device: Modius Stress
Common or usual name: Modius Stress
Classification name: Cranial Electrotherapy Stimulator (CES)
Regulatory Class: II
Product Code: QJQ
Regulation number: 882.5800
Classification panel: Neurology

III. Predicate devices

Primary predicate device

Modius Stress K232253
Summary

CES Ultra, K062284

Secondary predicate device

Alpha-Stim® CS, K903014

No reference devices were used in this submission.

IV. Device description

Modius Stress is a non-invasive transdermal neurostimulation device to treat the symptoms of Generalized Anxiety Disorder. The proposed mechanism of the device is through a technology known as Cranial Electrotherapy Stimulation (CES).

It consists of a battery-powered device designed to transcutaneously deliver low-level electrical energy (up to 1.5mA) to the skin behind the ears, over the mastoid processes. The delivery of this neurostimulation is through two self-adhesive electrode pads. These pads are placed on the skin behind each ear (mastoid area). The intensity of the electric pulse can be adjusted up or down by the user. When turned on, the device delivers a small electrical impulse, and adjustments to the stimulation level may be made using the up and down buttons on the device, which are located just above the power button. The device can also be paused by pressing the power button twice. When finished the user removes the device and disposes of the electrode pads after each use. When the device is not being used it can be charged through a micro-USB cable. For safety reasons, it is not possible to recharge the battery while the device is in use in stimulation mode.

The key components of the Modius Stress include the Modius Stress device (plastic enclosure and printed circuit board assembly (PCBA), stimulation pads (K210448 and K132588), skin cleansing wipes (K121655) and charging accessories. The PCBA consists of a microcontroller, USB connector, transformer driver, IO expander and EEPROM memory. The embedded software within the device manages overall functionality of the device from Stimulation Control, Power Management, and user interaction (Indication LED and Audio tones).

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Biocompatibility testing in accordance with the endpoints of ISO 10993-1 to be addressed for a surface medical device, with prolonged: > 24 hours less than 30 days contact duration, demonstrated good biocompatibility for all components of the Modius Stress device.

Device Usage

Using the Modius Stress device has demonstrated an improvement in the symptoms of Generalized Anxiety Disorder (GAD).

After using Modius Stress there are usually no physical limitations imposed so most users can resume normal activities immediately. Some users may have a response that affect their ability to perform potentially hazardous tasks, such as operating a motor vehicle or heavy machinery for up to several hours after treatment. However, no significant lasting side effects have been reported.

V. Indications for use

Modius Stress is a non-invasive, home-use neurostimulation device that is indicated to treat the symptoms of Generalized Anxiety Disorder in adults aged 22 and older, when used for approximately 4 weeks. Durability of effect after 4 weeks has not been established.

VI. Comparison of the technological characteristics with the predicate device

Modius Stress is substantially equivalent with respect to indications for use, stimulation parameters (i.e., current levels, frequencies, pulse width and amplitude) and electrode placement to the predicate devices CES Ultra (cleared by K062284), and Alpha-Stim® CS (cleared by K903014).

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Summary

Table 1. Summary of substantial equivalence

Property	Proposed Device	Primary Predicate	Secondary Predicate	Comment
Device	Modius Stress	CES Ultra	Alpha-Stim® CS	N/A
Indications for Use	Modius Stress is a non-invasive, home-use neurostimulation device that is indicated to treat the symptoms of Generalized Anxiety Disorder in adults aged 22 and older, when used for approximately 4 weeks. Durability of effect after 4 weeks has not been established.	The CES Ultra is indicated for the treatment of insomnia, depression or anxiety	The Alpha-Stim® 100 is a precision medical instrument used for the management of pain, anxiety, depression, and/or insomnia.	Predicate devices are indicated for the treatment of anxiety and in the case of Modius Stress for symptoms of Generalized Anxiety Disorder.
Target Population	Adults 22 and older	Adults	Adults	N/A
Environment	Home	Home	Home	N/A
Waveform	Symmetrical Biphasic Rectangular Wave	Symmetrical Biphasic Rectangular Wave	Symmetrical Biphasic Rectangular Wave	Identical
Current Intensity Range	0μA – 1500μA	0μA – 1500μA continually adjustable	0μA – 500μA	Modius Stress and the CES Ultra have near identical current intensity ranges

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Property	Proposed Device	Primary Predicate	Secondary Predicate	Comment
Pulse Width Range	2.5ms	2ms	250ms – 1s	Pulse width varies depending on frequency range
Number of electrodes	Two	Two	Two	Identical
Electrode placement	Mastoid	Mastoid or earlobes	Head – earlobes	The Modius Stress electrodes are placed on mastoids. CES Ultra also supports mastoid only electrode placement
Power Source	3.75 Lithium Polymer Battery	9V Alkaline Battery	2 x AAA NiMH	
Frequency	100Hz	100Hz	0.5Hz, 1.5Hz, 100Hz	
Treatment Range	30 min	30min, 60min or continuous	10min, 20min, 60 min or continuous	Modius Stress maximum treatment time is within the range of the predicates
Unit Controls	Built into the device	Built into the device	Built into the device	Identical
Dimensions	16.5cm x 15.1cm x 6.6cm	13.5cm x 6.4cm x 3.3cm	9.8cm x 6.3cm x 2cm	Modius Stress is larger than the predicate devices
Enclosure	Plastic	Plastic	Plastic	Identical

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Table 2. Safety Information Comparison

Property		*Proposed Device* Modius Stress	*Primary Predicate* CES Ultra	*Secondary Predicate* Alpha-Stim® CS	Comment
Electrical Safety		Complies with IEC 60601-1	Complies with IEC 60601	Complies with IEC 60601	The proposed device and predicate devices are identical
EMC		Complies with IEC 60601-1-2	Complies with IEC 60601-1-2	Complies with IEC 60601-1-2	The proposed device and predicate devices are identical
Software	**Level of Concern**	Moderate	Moderate	Moderate	The proposed device and predicate devices are identical
	Verification & Validation	Complies with FDA Guidance Requirement	Complies with FDA Guidance Requirement	Complies with FDA Guidance Requirement	
Biocompatibility		Complies with ISO 10993	Complies with ISO 10993	Complies with ISO 10993	The proposed device and predicate devices are identical

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Table 3. Technical Information for the Modius Stress Output parameters

	Modius Stress	CES Ultra	Alpha-Stim CS
510(k) Number	K232253	K024377	K903014
Device Name	Modius Stress	CES ultra	Alpha-Stim CS
Manufacturer	Neurovalens Ltd	Neuro-Fitness LLC	Electromedical Products Inc.
Power Source†	3.75 Lithium Polymer Battery	9V Alkaline Battery	2 x AAA NiMH
-Method of Line Current Isolation	DC:DC transformer	N/A Non Rechargeable	N/A Non-Rechargeable
- Patient Leakage Current (as per ANSI/AAMI 60601-1)	0µA	Unknown	Unknown
-Normal Condition (µA)	0-1500µA	0-1500µA	0-500µA
-Single Fault Condition (µA)	2.3µA	Unknown	1.3mA
Average DC current through the electrodes when the device is on but no pulses are being delivered (µA)	0µA	Unknown	Unknown
Number of output channels	1	1	1
-If more than one channel, is the stimulus delivered to each channel synchronous or alternating between each channel?	N/A	N/A	N/A
-If more than one channel, describe method of channel isolation	N/A	N/A	N/A
Software/Firmware/Microprocessor Control	Yes	Yes	Yes
Automatic Overload Trip?	No	No	No

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		Modius Stress	CES Ultra	Alpha-Stim CS
Automatic Shut Off?		Yes	Yes	Yes
User Override Control?		Yes	Yes	Yes
Mode or Program Name		Stimulation mode	Stimulation mode	Stimulation/Treatment Mode
Waveform (e.g., pulsed monophasic, biphasic)		Biphasic	Biphasic	Biphasic
Shape (e.g., rectangular, spike, rectified sinusoidal)		Rectangular	Rectangular	Rectangular
Maximum Output Voltage (volts) (+/-1%)		750mV @500 Ω	Unknown	@500 Ω
		3V @ 2 kΩ	Unknown	@ 2 kΩ
		15V @10 kΩ	Unknown	@10 kΩ
Maximum Output Current (specify units) (+/-2%)		1500µA @500 Ω	Unknown	500µA @ 500 Ω
		1500µA @ 2 kΩ	1.5mA @ 2kΩ	@ 2 kΩ
		1500µA @10 kΩ	Unknown	@10 kΩ
Duration of primary (depolarizing) phase† (msec)		10ms	10ms	2000ms, 1000ms, 10ms
Pulse Duration†† (msec)		5ms	5ms	1000ms, 500ms, 5ms
Frequency†† (Hz) [or Rate†† (pps)]		100Hz	100Hz	0.5Hz, 1Hz, 100Hz
For interferential modes only: Beat Frequency† (Hz)		Not Applicable for these devices		
For multiphasic waveforms only:	**Symmetrical phases?**			
	Phase Duration† (include units), (state range, if applicable), (both phases, if asymmetrical)			

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		Modius Stress	CES Ultra	Alpha-Stim CS
Net Charge (microcoulombs (mC) per pulse) (If zero, state method of achieving zero net charge.)		3.75µC @2k Ω / 3.75 µC @ 500 Ω	0.75µC @500 Ω	300µC, 150 µC, 1.5 µC
Maximum Phase Charge, (µC)		3.75µC @2k Ω / 3.75 µC @ 500 Ω	0.75µC@ 2 kΩ	600µC @ 500Ω
Maximum Current Density,†††† (mA/cm², r.m.s.)		0.75mA /cm^2 @500 Ω	1.91mA/cm^2 @500 Ω	~1.2mA/cm^2 @ 500Ω
Maximum Average Current (average absolute value), mA		1.5mA @500 Ω 1.5mA @ 2kΩ	3.07mA/cm^2 @ 2 kΩ	Unknown
Maximum Average Power Density,†††† (W/cm²), (using smallest electrode conductive surface area)		0.28mW/cm^2 @500Ω 2.24mW/cm^2 @2kΩ	9.19mW/cm^2 @2 kΩ	Unknown
Burst Mode†††† (i.e., pulse trains):	**(a) Pulses per burst**	2	2	2, 2, 2
	(b) Bursts per second	100	100	0.5, 1, 100
	(c) Burst duration (seconds)	0.01	0.01 (10ms)	2, 1, 0.01s
	(d) Duty Cycle: Line (b) x Line (c)	0.5 (50%)	0.2(20%)	0.5 (50%)
ON Time (seconds)		5ms	10ms	1sec, 0.5sec, 10ms
OFF Time (seconds)		5ms	40ms	1sec, 0.5sec, 10ms

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Table 4. Comparison of Device Outputs

Output value	Modius stress	CES Ultra	Alpha Stim CS
Load conditions **Output value at 500Ω, 2kΩ and 10kΩ**	1.5mA at all loads	1.5mA at all loads	0.6mA at all loads
Electrode surface area in cm2	Conductive Area (16mm diameter) 2.0cm^2	Ear clips Diameter 7.9mm 0.5cm^2 Area	1.5cm Diameter 1.77cm^2
Current density	**500Ω** 0.75mA/cm^2, **2kΩ** 0.75mA/cm^2 **10kΩ** 0.75mA/cm^2	**500Ω** 1.91mA/cm^2 **2kΩ** 3.07mA/cm^2 **10kΩ** Unknown	**500Ω** 1.2mA/cm^2 **2kΩ** Unknown **10kΩ** Unknown
Charge density	**500Ω** 1.87µC – Per Pulse **2kΩ** 1.87µC – Per Pulse **10kΩ** 1.87µC – Per Pulse	**500Ω** Unknown **2kΩ** Unknown **10kΩ** Unknown	**500Ω** Unknown **2kΩ** Unknown **10kΩ** Unknown
Power density	**500Ω,** 0.56mW/cm^2 **2kΩ** 2.24mW/cm^2 **10kΩ** 11.19mW/cm^2	**500Ω,** Unknown **2kΩ** 9.19ma/cm^2 **10kΩ** Unknown	**500Ω,** Unknown **2kΩ** Unknown **10kΩ** Unknown
Max phase charge (pulse width x peak current)	**500Ω,** 3.75 µC – Per Pulse **2kΩ** 3.75 µC – Per Pulse **10kΩ** 3.75 µC – Per Pulse	**500Ω,** Unknown **2kΩ** 0.75 µC **10kΩ** Unknown	**500Ω,** 600 µC **2kΩ** Unknown **10kΩ** Unknown
Max phase charge density (pulse width x peak current) / electrode surface area	**500Ω** 1.87µC – Per Pulse **2kΩ** 1.87µC – Per Pulse	**500Ω** Unknown **2kΩ** Unknown	**500Ω** Unknown **2kΩ** Unknown

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	10kΩ 1.87µC – Per Pulse	**10kΩ** Unknown	**10kΩ** Unknown
Max average power density (Duty cycle x peak current)^2 x (load Ω) ÷ electrode surface area)	**500Ω,** 0.28mW/cm^2 **2kΩ** 1.12mW/cm^2 **10kΩ** 5.6mW/cm^2	**500Ω,** Unknown **2kΩ** 9.19mW/cm^2 **10kΩ** Unknown	**500Ω,** Unknown **2kΩ** Unknown **10kΩ** Unknown

VII. Performance Data

Non-clinical tests

The Modius Stress was evaluated for its safety and effectiveness based on the following testing:

Table 5: Non-clinical tests

Test Name	Test Description	Results
Device Ship/Transport Testing	Ensure device, enclosed in the selected shipping container, meets ASTM D4169 specifications.	Passed
Biocompatibility Testing	Testing and analysis of the Modius Stress device has demonstrated compliance to ISO 10993-1: Biological evaluation of medical devices – Guidance	Passed
Electrical Safety	The Modius Stress device was tested to confirm that it met the applicable standards for electrical safety (IEC 60601-1)	Passed
EMC	The Modius Stress device was tested to confirm that it met the applicable standards for electromagnetic compatibility (EMC) (IEC 60601-1-2)	Passed
Usability Testing	Modius Stress was assessed with regards to usability for compliance with IEC 62366 – Medical devices – Application of usability engineering to medical devices	Passed
Maximum Current & Phase Charge Testing	The Maximum Current & Phase Charge Testing was to detail the Max Current / Power output of the system under different load conditions and determine the Max Phase Charge, Max Current Density and Max Power Density of the Modius Stress device.	Passed
System Verification and Validation Testing	The system verification and validation testing was performed to verify the hardware and firmware of the Modius Stress Device	Passed

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Labeling

The labeling for the device includes the intended use population and the intended use environment; warning that patients should be monitored by their physician for signs of worsening; A warning that instructs patients on how to mitigate the risk of headaches, and what to do should a headache occur; a warning that instructs patients on how to mitigate the risk of dizziness, and what to do should dizziness occur; a detailed summary of the clinical testing, which includes the clinical outcomes associated with the use of the device, and a summary of adverse events and complications that occurred with the device; Instructions for use that address where to place the electrodes, what stimulation parameters to use, and duration and frequency of treatment sessions based on the results of clinical studies for the device; A detailed summary of the device technical parameters, including waveform, output mode, pulse duration, frequency, train delivery, and maximum charge and energy; and Information on validated methods for reprocessing any reusable components between uses.

Software Verification and Validation Testing

Software verification and validation testing were conducted, and documentation was provided as recommended by FDA's Guidance for Industry and FDA Staff, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices."

The software for this device was considered as a "moderate" level of concern, since a failure or latent design flaw could directly result in minor injury to the patient or operator or a failure or latent flaw could indirectly result in minor injury to the patient or operator through incorrect or delayed information or through the action of a care provider.

Animal Studies

No animal studies were conducted as part of submission to prove substantial equivalence.

Clinical Studies

CES devices collectively demonstrate a class effect of CES for treating anxiety and/or insomnia. However, it cannot be concluded, based on available information alone, that specific CES devices or stimulation parameters are effective for treating anxiety and/or insomnia. As such, individuals using this device should work with the prescribing medical provider to

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determine the best treatment settings to use. As such, please see General CES Summary below for a general summary of pertinent clinical literature that has been published using various combinations of CES devices, stimulation settings, and electrode positions.

General CES Summary (January 01, 1970, to November 2022)

As of November 2022, 33 studies investigated the impact of Cranial Electrotherapy Stimulation (CES) on anxiety (14 randomized controlled trials (RCTs), 13 observational studies, 2 metaanalysis, and 4 reviews). Of the RCTs that were evaluated, some trials reported superiority of CES treatment versus placebo (Rosenthal, S H et al. 1972) (Philip, P et al. 1991) (Lee, S H, et al. 2013) (Sousa, A D et al. 1975) (Gibson, T H et al. 1987) (Ryan, J J. et al. 1976) (Kim, J, et al. 2021) or control (Kang, H W, et al. 2020) (Park, B S, et al. 2022) in reducing anxiety symptoms, while other studies demonstrated no impact on anxiety (Levitt, E A et al. 1975) (Passini, F G et al. 1976) (Scallet, A, et al. 1976) (13). One study noted transient improvement in symptoms (Hearst, E D, et al. 1974). The majority of observational studies reported a positive association between CES treatment and reduction in anxiety symptoms (Flemenbaum, A et al. 1974,) (Overcash, S J. et al 1999) (Rosenthal, S et al. 1970) (Rosenthal, S H et al. 1970) (Smith, R B et al. 1999) (Ryan, J J et al. 1977) (Matteson, M T et al. 1986) (Morriss, R, et al. 2019) (Morriss, R, et al. 2020) (Bystritsky, A, et al. 2008). One observational study reported that CES was as effective as usual care (Royal, S, et al., 2022). Only 2 observational studies reported that CES did not have a significant impact on anxiety based on clinical assessment and standard inventories (Moore, J A, et al. 1975) (Von Richthofen et al 1980). A meta-analysis of 10 studies evaluating the effectiveness of cranial stimulation in treating depression noted an effect on anxiety as a secondary study outcome compared to sham (Cheng, Y, et al. 2022). Another meta-analysis of 14 RCTs evaluating the effectiveness of cranial stimulation indicated that CES versus sham treatment was associated with significantly improved anxiety (Klawansky, S, et al. 1995).

Similar findings were reported in a review that examined 34 controlled trials involving a total of 767 patients receiving CES and an additional 867 patients serving as controls (De Felice, E A. 1997). Twenty-six (Moore, J A, et al. 1975,) of 34 studies (77%) reported decreased anxiety after treatment with CES and the remaining 8 of 34 studies (24%) reported no such benefit. Two other reviews of trials using CES in patients with anxiety and depression concluded that CES may provide a modest benefit in the treatment of anxiety (31) (Brunyé, T

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T, et al. 2021). A fourth review found several small studies reporting decreased anxiety with CES use in patients with various conditions, including 1 small study in individuals with anxiety disorder (Freire, R C, et al. 2020). In studies that reported improvement in anxiety with use of CES, the reported stimulation parameters, electrode placement, and treatment schedule varied widely as listed below and were only evaluated in a small number of combinations. Please also note that not all CES devices are capable of providing the same stimulation parameters or combination of stimulation parameters.

Electrode placement:

- Over orbits and mastoids
- Over eyelid and mastoids
- Over orbits and occiput
- Earlobes
- Anterior and posterior regions of the head; in ear

Waveform:

- Square
- Rectangular
- Monophasic
- Bipolar, asymmetric, rectangular waves
- Sine wave
- Biphasic modified square wave
- Modified sine wave

Frequency:

- 100 Hertz (Hz)
- 350 Hz
- 0.5 Hz
- 10 Hz

Pulse Width:

- 0.7 millisecond (ms)
- 1 ms
- 2 ms

Maximum current:

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- 0.01-4 milliamperes (mA)

Treatment schedule:

- 30 minutes, 5 times a week for 1-2 weeks
- 30-minute sessions twice a day
- single 20-minute session
- 5 times a week for 3 weeks
- 20 minutes a day for 2 days
- 60 minutes a day for 6-12 weeks
- 5 minutes
- 45 minutes daily for 3 weeks

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Modius Stress – Clinical Studies

A summary of the clinical performance testing is given below with detailed information provided in Section 20.

Clinical testing of the Modius Stress device (MA1500) included two pivotal randomized controlled trials to evaluate the safety and efficacy of the Modius Stress device, for the treatment of anxiety. Originally a multi-site study was planned; however, logistical challenges prevented the research site in India from adhering to the precise study design outlined in the UK protocol. As a result, the studies are documented separately.

The stimulation sessions received at the India site were of the same duration (30 minutes) as the sessions participants completed at home in the UK. UK participants were instructed to use their device daily or no less than 5 times per week; however, at the India site, participants were asked to complete 20 stimulation sessions at a rate of ~3 -5 sessions per week. The difference in the treatment duration was to allow flexibility to facilitate the additional travel and time spent going to the India research site.

Study Design

Both studies were randomised, double blinded, sham-controlled trials, one of which was conducted in the UK and the other in India. The UK study was undertaken from July 2022 to April 2023 and has been registered at https://clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT05907967). The UK study protocol (version 6.0, 25/11/2022) was approved at the UK site by East of England – Cambridge Central Research Ethics Committee (Ref: 22/EE/0009). The study in India was conducted from October 2022 to June 2023 and has also been registered at ClinicalTrials.gov (Identifier: NCT05845658). The Indian study protocol (version 1.0, 25/07/2022) was approved by the Institutional Ethics Committee – R.D.Gardi Medical College, Ujjain, Madhya Pradesh, India (Ref: 14/2022). Informed consent was obtained from all participants.

In both studies, adults with a General Anxiety Disorder 7th edition (GAD-7) score of 10 or higher (Spitzer et al., 2006) were recruited using social media advertising and were randomly

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allocated (1:1 allocation ratio) to receive the Modius Stress device (intervention group) or the sham device (active control group). In the UK study, both groups were advised to use their allocated devices for 30 minutes per day for a four-week duration at home. In the India study, both groups were asked to complete 20 stimulation sessions (30 minutes duration) at a rate of ~3-5 sessions per week at the Department of Physiology at R.D. Gardi Medical College.

The Modius stress and sham devices are identical in appearance and therefore neither the participant nor the clinical study team knew whether the Modius Stress device or sham device was allocated.

Primary Effectiveness Endpoint

The efficacy of the Modius Stress device was quantified by change in GAD-7 score at baseline and week 4 in the UK study, and when each participant finished their 20 stimulation sessions in the India study, between the Modius Stress group and sham control group.

Primary Safety Endpoint

In both studies, an evaluation of the safety of the Modius Stress device was quantified by the occurrence in adverse events between the Modius Stress group and sham control group.

UK study results

A total of 87 eligible participants (female, n=65) were recruited and randomised to the Modius Stress group (n=43) or the sham control group (n=44). Nine participants withdrew from the study before the 4-week visit. Three of these participants withdrew (lost to follow-up, n=2 and self-withdrawal, n=1) prior to the baseline visit and therefore were not included in the Intention to treat (ITT) analysis (no baseline data and did not receive at least one stimulation session). The mean age of the sample was 30 years (age range: 18 to 69 years). One participant was aged over 65 years, and 14 participants were aged under 22 years.

Table 6: Participant accountability (UK study)

Stage	Modius Stress Device	Sham control device	Total
Enrolment	43	44	87
Treatment	42	42	84

Primary safety endpoint analysis	42	42	84
Primary effectiveness endpoint analysis	[a]Intention to treat= 42 [b]Complete case = 36	Intention to treat = 42 Complete case = 39	84 75

[a]Intention to treat analysis was undertaken for all participants who were randomised and had baseline GAD-7 scores. [b]Complete case analysis was undertaken on all participants with available data at baseline and at the 4-week visit.

Effectiveness

The effect of the Modius Stress device on change in GAD-7 scores from baseline to the 4-week visit is shown in Table 7 below. The ITT (multiple imputation (MI) and baseline carried forward (BOCF)) and complete case analyses demonstrated that the Modius Stress group had a greater reduction in GAD-7 score compared with the sham control group; however, the mean difference among the groups was not statistically different.

More participants in the Modius Stress group, compared with the sham control group, achieved a 4 point or more reduction in GAD-7 (Toussaint et al., 2020) from baseline to the 4-week visit (complete case analysis: 27 out of 36 [75%] vs 20 out of 39 [51%]).

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Table 7. The effect of Modius Stress on GAD-7 scores according to randomization group (primary outcome) (UK Study)

	Modius Stress			Sham Control				
Cohort	**Baseline Mean (SD)**	**4 weeks Mean (SD)**	**Within-group mean change (95% CI)**	**Baseline Mean (SD)**	**4 weeks Mean (SD)**	**Within-group mean change (95% CI)**	**Between-group difference mean (95% CI)[a]**	**P**
ITT (MI)	11.36 (0.66)	5.95 (0.59)	-5.41 (-6.83, -3.99)	10.90 (0.54)	6.94 (0.59)	-3.96 (-5.25, -6.06)	-1.45 (-3.37, 0.47)	0.139
ITT (BOCF)	11.36 (4.27)	6.83 (4.03)	-4.52 (-5.91, -3.14)	10.90 (3.47)	7.10 (3.75)	-3.81 (-5.08, -2.54)	-0.71 (-2.57, 1.14)	0.445
Complete Case	11.17 (4.32)	5.89 (3.20)	-5.28 (-6.75, -3.80)	11.15 (3.31)	7.05 (3.74)	-4.10 (-5.43, -2.78)	-1.18 (-3.12, 0.77)	0.233

[a]Between-group difference in GAD-7 scores from baseline to week 4 analysed using Independent Samples t-tests. ITT analysis (MI and BOCF) includes all participants randomized and who had baseline GAD-7 scores (Modius Stress, n=42 and sham control n=42). Three participants did not have baseline GAD-7 scores and were not included in the ITT analysis. Complete case analysis includes participants who had baseline and 4-week GAD-7 scores (Modius Stress n=36 and sham control n=39).

Safety

A total of 7 Adverse Events were reported during the 4-week study, 5 reported by the Modius Stress group and 2 reported by the sham control group. The adverse events were all minor, caused a minimal discomfort to participants, and all self-resolved during the period of the study. No serious adverse events were reported.

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Table 8. Number (%) of Adverse Events (Safety Data Analysis) according to Randomization Group (all participants, n=87) (UK Study)

		Total n (%)	Modius Stress n (%)	Sham Control n (%)
Nervous System Disorders	Migraine	1 (1)	1 (1)	0 (0)
	Sudden sharp movements	1 (1)	0 (0)	1 (1)
	Cartilage swelling	1 (1)	1 (1)	0 (0)
Ear Disorders	Itchiness	1 (1)	1 (1)	0 (0)
	Pressure in ears	1 (1)	1 (1)	0 (0)
Mouth/ dental disorders	Metallic fillings pulsing/ buzzing	1 (1)	0 (0)	1 (1)
Other	Study related anxiety	1 (1)	1 (1)	0 (0)

Conclusion

Participants using the Modius Stress device, 5-7 times per week, had a 5.41 reduction in GAD-7 score, while participants using the sham control device had a 3.96 reduction in GAD-7 score. More participants using the Modius Stress device daily had a 4-point or more reduction in GAD-7 score when assessed at 4 weeks.

India study results

A total of 60 eligible participants were recruited and randomised to the Modius Stress group (n=34) or the sham control group (n=26). One participant randomised to the sham control group withdrew from the study due to difficulty attending the research site for treatment and assessments. The mean age of the sample was 35.6 years. The age range was 19-70 years, with one participant aged over 65 years and two participants aged under 22 years.

Table 9: Participant accountability (India study)

Stage	Modius Stress Device	Sham control device	Total
Enrolment	34	26	60
Treatment	34	26	60
Primary safety endpoint analysis	34	26	60
Primary effectiveness endpoint analysis	[a]Intention to treat= 34 [b]Complete case = 34	Intention to treat = 26 Complete case = 25	60 59

[a] Intention to treat analysis was undertaken for all participants who were randomised and had baseline GAD-7 scores. [b]Complete case analysis was undertaken on all participants with available data at baseline and at end of study assessment.

Effectiveness

The study met the primary endpoint. The Modius Stress group had a mean reduction in GAD-7 score of -7.44 ($p<0.001$) while the sham control group reduced their GAD-7 mean score by -2.23 ($p=0.002$). The mean difference between the groups was statistically significant (ITT, mean difference: -5.21 [95% CIs: -6.57, -3.85]; $p<0.001$).

Furthermore, more participants in the Modius Stress group, compared with the sham control group, achieved a 4 point or more reduction in GAD-7 from baseline to the follow up visit (33 out of 34 [97%] vs 6 out of 25 [24%]).

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Table 10. The effect of Modius Stress on GAD-7 scores according to randomization group (India Study)

	Modius Stress			Sham Control				
Cohort	**Baseline Mean (SD)**	**20 sessions Mean (SD)**	**Within-group mean change (95% CI)**	**Baseline Mean (SD)**	**20 sessions Mean (SD)**	**Within-group mean change (95% CI)**	**Between-group difference mean (95% CI)**	**P**
ITT (BOCF)	12.71 (1.59)	5.26 (2.06)	-7.44 (-8.12, -6.76)	12.77 (1.48)	10.54 (3.17)	-2.23 (-3.56, -0.91)	-5.21 (-6.57, -3.85)	<0.001
Complete Case	12.71 (1.59)	5.26 (2.06)	-7.44 (-8.12, -6.76)	12.88 (1.39)	10.56 (3.23)	-2.32 (-3.69, -0.95)	-5.12 (-6.63, -3.62)	<0.001

[a]Between-group difference in GAD-7 scores from baseline to end of study (completion of 20 stimulation sessions) analyzed using Independent Samples t-tests. ITT analysis (BOCF) includes all participants randomized and who had baseline GAD-7 scores (Modius Stress, n=34 and sham control n=26). Complete case analysis includes participants who had baseline and end of study (completion of 20 stimulation sessions) GAD-7 scores (Modius Stress n=34 and sham control n=25).

Safety

No causally related adverse events or serious adverse events were reported by the Modius Stress group or the sham control group during the study period.

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Conclusion

ITT and complete case analyses of the pivotal study demonstrates that participants using the Modius Stress device for 20 sessions had a significantly greater reduction in GAD-7 score, compared with the sham group. Additionally, more participants using the Modius Stress had a 4-point or more reduction in GAD-7 score compared to the sham group, when assessed after 20 sessions.

Study Limitations

As with all clinical trials, confounding factors can make it difficult to interpret how well the intervention has worked. Therefore, to ensure a robust dataset with a low number of variables, several conditions and medications were excluded in this clinical trial.

- Persons currently taking over the counter or prescribed medications for anxiety, antidepressant medications, beta blockers, or who regularly use antihistamines.
- Persons with a history of stroke, or severe injury to the brain.
- Persons with a cognitive impairment.
- Persons with any disease which may cause vestibular neuropathy.
- Persons with myelodysplastic syndromes, or history of malignancy in the past
- 12-months.
- In the UK study, with the same protocol, participants using the Modius Stress device, 5-7 times per week, had a 5.41 reduction in GAD-7 score, while participants using the sham device had a 3.96 reduction in GAD-7 score, when assessed at 4-weeks. While the Modius Stress group had a greater reduction in GAD-7 score compared with the sham control group, the primary endpoint was not met i.e., the mean difference among the groups was not statistically different. In contrast, the mean difference between the groups was statistically significant in the India study. The difference in results between the two studies is a limitation when extrapolating clinical meaning from this study.

Three participants in the UK study who were excluded from the ITT analysis were randomised (active device, n=1 and sham device, n=2); however, they were withdrawn from the study (self-withdrawal, n=1 and LTF, n=2) prior to the baseline visit (no baseline or follow-up data) and failed to complete at least one stimulation session using their allocated device (that includes the training session). As the participants were blinded to their device allocation, the

decision of whether or not to begin treatment could not be influenced by knowledge of the assigned treatment.

Generalizability of Study Data

The Modius Stress trial consisted of two separate clinical studies, with one based in the United Kingdom (UK) and the other in India. It should be noted that the UK site received ethical approval to recruit remotely, and additionally this extended to include remote recruitment across The Republic of Ireland (ROI). Therefore, three populations were included in the Modius Stress study, with two of these populations being recruited nationwide (as opposed to the proximity of the clinical site). Both the UK and India study protocols had the same inclusion criteria of a GAD-7 score of 10 or greater at screening.

As described in more detail above, the two studies were analyzed separately due to different endpoints for the primary effectiveness outcome. The UK study analysis demonstrated that while the Modius Stress group had a greater reduction in GAD-7 score compared with the sham control group, the mean difference among the groups was not statistically different. In contrast the India study analysis did demonstrate that participants using the Modius Stress device for 20 sessions had a significantly greater reduction in GAD-7 score. Due to the difference in results between the two studies, there is some uncertainty when considering the generalizability of the findings.

Post-hoc Subgroup Analysis

As mentioned previously, to test the clinical performance of the Modius Stress device, a multi-site study including a site in the UK and a site India was initially planned. However, the research site in India was unable to follow the exact study design as described in the UK protocol due to logistical issues (lack of home internet access). Therefore, participants had to travel to the research site in India to receive the stimulation sessions (20 sessions, completed at a rate of 3-5 daily sessions per week); whereas in the UK, participants received the stimulation at home (5-7 daily sessions completed by week 4). This resulted in the studies differing in terms of duration. Consequently, the studies were undertaken and reported separately.

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Furthermore, when developing the protocol for this pivotal trial, it was hypothesised that individuals with a GAD-7 score of 10 or greater at baseline allocated to the Modius Stress group would achieve a greater reduction in GAD-7 compared with the sham control group at 4 weeks. However, it was noted that some of the UK participants reported GAD-7 scores below 10 at baseline. The lack of statistical difference in GAD-7 scores between the randomised groups at the UK site as reported above, was possibly due to the inclusion of several participants who did not report having moderate to severe GAD at baseline; this warranted further investigation.

The below observational post hoc analysis was performed to better understand any potential benefit to participants suffering from Generalized Anxiety Disorder. This post hoc analysis was not included in the study's statistical analysis plan; therefore, the descriptive outcomes provided are exploratory.

The post hoc sub-group analysis (including India and UK participants) was therefore undertaken to analyse the data according to the UK protocol (initial study design). The analysis included participants who completed their stimulation sessions by 4 weeks and had a GAD-7 score at baseline of 10 or greater.

A total of 25 participants (Modius Stress, n=15 and sham control, n=10) at the India site and 48 participants (Modius Stress, n=23 and sham control, n=25) at the UK site met the above criteria and were included in the post hoc analysis to investigate the effect of the Modius Stress device on change in GAD-7 scores at 4 weeks.

In each of the two sub-samples analysed, the group who were allocated the Modius Stress device had a greater mean reduction in GAD-7 compared with the sham control group. In the UK subgroup, participants using the Modius Stress device, had a 7.44 (95% CI: -8.87, -6.00) reduction in GAD-7 score, compared to participants using the sham device who had a 5.36 (95% CI: -7.06, -3.66) reduction in GAD-7. In the India subgroup, participants using the Modius Stress device, had a 6.67 (95% CI: -7.93, -5.40) reduction in GAD-7 score, compared to participants using the control device who had a 1.90 (95% CI: -4.20, 0.40) reduction in GAD-7 score.

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Limitations of post-hoc analysis

While the above post-hoc subgroup analysis is only exploratory the approach used is aligned with the original protocol (UK protocol) developed to test the efficacy and safety of the Modius Stress device. When developing the protocol for this study, it was hypothesized that individuals with a GAD-7 score of 10 or greater at baseline allocated to the Modius Stress group would achieve a greater reduction in GAD-7 compared with the sham control group at 4 weeks.

The two studies had different study durations because of the lack of home internet access in India and the smartphones not being able to support the study app; therefore, the results for the sites were analysed separately due to this heterogeneity. The post-hoc subgroup analysis includes participants at the India site who completed the 20 stimulation sessions at 4 weeks and the UK participants who completed their stimulation sessions at 4 weeks. This approach generates similarity among the studies.

VIII. Safety and Effectiveness Conclusion

Based on the clinical performance as documented in the two pivotal clinical studies described above, Modius Stress is a low-risk, non-invasive, drug-free therapy, that provides a benefit when used to treat symptoms of Generalized Anxiety Disorder.

Based on this clinical testing and technical comparison, it can be determined that Modius Stress device is substantially equivalent to the listed predicate devices.

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