October 27, 2023

Neurovalens Limited
Jason McKeown, MD
CEO
8 Carmagrim Road
Portglenone, BT44 8BP
United Kingdom

Re: K230826
Trade/Device Name: Modius Sleep
Regulation Number: 21 CFR 882.5800
Regulation Name: Cranial electrotherapy stimulator
Regulatory Class: Class II
Product Code: QJQ
Dated: March 21, 2023
Received: March 24, 2023

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)*
K230826

Device Name

Modius Sleep

Indications for Use *(Describe)*

Modius Sleep is a non-invasive, home-use neurostimulation device that is indicated to treat chronic insomnia in adults aged 22 and older.

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.

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510(k) Summary

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

I. Submitter

Neurovalens Limited
8 Carmagrim Road
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United Kingdom

Contact person/ official correspondence:
Dr Jason McKeown
CEO Neurovalens Ltd.
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Email: Jason.mckeown@neurovalens.com

Date Prepared
27th October 2023

II. Device

Name of Device: Modius Sleep
Common or usual name: Electrical Vestibular Nerve Stimulator (VeNS)
Classification name: Cranial Electrotherapy Stimulator (CES)
Regulatory Class: II
Product Code: Requested
Regulation number: 882.5800
Classification panel: Neurology
Special Controls: Modius Sleep complies with the special controls as set in FDA 21 CFR 882.5800 for a Class II, Cranial Electrical Stimulation (CES) device.

III. Predicate devices

Primary predicate device

CES Ultra, K062284

Secondary predicate device

Alpha-Stim® CS, K903014

No reference devices were used in this submission.

IV. Device description

Modius Sleep is a low-risk non-invasive transdermal neurostimulation device to treat chronic insomnia. The proposed mechanism of the device is through a technology known as electrical vestibular nerve stimulation (VeNS).

It consists of a battery-powered device designed to transcutaneously deliver low-level electrical energy (up to 1mA) 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 which stimulates the vestibular nerve. 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.

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The key components of the Modius Sleep include the Modius Sleep 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 (charging only), 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).

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 Sleep device.

Device Usage

Daily sessions of Modius Sleep has been shown to improve insomnia when assessed at 4 weeks.

After using Modius Sleep 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 Sleep is a non-invasive, home-use neurostimulation device that is indicated to treat chronic insomnia in adults aged 22 and older.

VI. Comparison of the technological characteristics with the predicate device

Modius Sleep 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).

510(k) Summary

Table 1. Summary of substantial equivalence

Property	Proposed Device	Primary Predicate	Secondary Predicate	Comment
Device	Modius Sleep	CES Ultra	Alpha-Stim® CS	
Indications for Use	Modius Sleep is a non-invasive, home-use neurostimulation device that is indicated to treat chronic insomnia in adults aged 22 and older.	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.	All devices are indicated for the treatment of insomnia.
Target Population	Adults 22 and older	Adults	Adults, and children under adult supervision	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 - 1000μA	0μA - 1500μA continually adjustable	0μA - 500μA	Modius Sleep and the CES Ultra have near identical current intensity ranges
Pulse Width Range	1s	2ms	250ms – 1s	Pulse width varies depending on frequency range
Number of electrodes	Two	Two	Two	Identical

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Property	Proposed Device	Primary Predicate	Secondary Predicate	Comment
Electrode placement	Mastoid	Mastoid or earlobes	Head - earlobes	The Modius Sleep 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	0.25Hz	100Hz	0.5Hz, 1.5Hz, 100Hz	
Treatment Range	30 min	30min, 60min or continuous	10min, 20min, 60 min or continuous	Modius Sleep 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 Sleep is larger than the predicate devices
Enclosure	Plastic	Plastic	Plastic	Identical

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Table 2. Safety Information Comparison

Property		*Proposed Device* Modius Sleep	*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 Modius Sleep Output Parameters

	Modius Sleep	CES Ultra	Alpha-Stim CS
510(k) Number	K230826	K062284	K903014
Device Name	Modius Sleep	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)	0-1000µA	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
Automatic Shut Off?	Yes	Yes	Yes

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		Modius Sleep	CES Ultra	Alpha-Stim CS
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%)		500mV @500 Ω	Unknown	@500 Ω
		2 V @ 2 kΩ	Unknown	@ 2 kΩ
		10V @10 kΩ	Unknown	@10 kΩ
Maximum Output Current (specify units) (+/-2%)		1000µA @500 Ω	Unknown	500µA @ 500 Ω
		1000µA @ 2 kΩ	1.5mA @ 2kΩ	500µA @ 2 kΩ
		1000µA @10 kΩ	Unknown	500µA @10 kΩ
Duration of primary (depolarizing) phase† (msec)		4000 (4 seconds)	10ms	2000ms, 1000ms, 10ms
Pulse Duration†† (msec)		2000 (2 second)	5ms	1000ms, 500ms, 5ms
Frequency†† (Hz) [or Rate†† (pps)]		0.25Hz	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 Sleep	CES Ultra	Alpha-Stim CS
Net Charge (microcoulombs (mC) per pulse) (If zero, state method of achieving zero net charge.)		1000 µC @2kΩ	0.75µC @500 Ω	300µC, 150 µC, 1.5 µC
Maximum Phase Charge, (µC)		1000µC @2kΩ	0.75µC@ 2 kΩ	500µC @ 500Ω
Maximum Current Density,†††† (mA/cm², r.m.s.)		0.5mA /cm^2 @500 Ω	1.91mA/cm^2 @500 Ω	~1.2mA/cm^2 @ 500Ω
Maximum Average Current (average absolute value), mA		1mA @2kΩ	3.07mA/cm^2 @ 2 kΩ	Unknown
Maximum Average Power Density,†††† (W/cm²), (using smallest electrode conductive surface area)		0.99mW/cm^2 @2 kΩ	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	0.25	100	0.5, 1, 100
	(c) Burst duration (seconds)	4	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)		2 sec	10ms	1sec, 0.5sec, 10ms
OFF Time (seconds)		2 sec	40ms	1sec, 0.5sec, 10ms

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Table 4. Comparison of Device Outputs

Output value	Modius Sleep	CES Ultra	Alpha Stim CS
Output value at 500Ω, 2kΩ and 10kΩ Load conditions	Provide for all load conditions. 1mA at all loads 0.25Hz	Provide for all load conditions. 1.5mA at all loads 100Hz	Provide for all load conditions. 0.5mA at all loads 0.5Hz
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** 0.5mA/cm^2, **2kΩ** 0.5mA/cm^2 **10kΩ** 0.5mA/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** 497.63μC/cm^2 – Per Pulse **2kΩ** 497.63μC/cm^2 – Per Pulse **10kΩ** 497.63μC/cm^2 – Per Pulse	**500Ω** Unknown **2kΩ** Unknown **10kΩ** Unknown	**500Ω** Max 500uC **2kΩ** Max 500uC **10kΩ** Max 500uC

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Power density	**500Ω,** 0.25mW/cm^2 **2kΩ** 0.99mW/cm^2 **10kΩ** 4.97mW/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,** 1000 µC – Per Pulse **2kΩ** 1000 µC – Per Pulse **10kΩ** 1000 µC – Per Pulse	**500Ω,** Unknown **2kΩ** 0.75 µC **10kΩ** Unknown	**500Ω,** 500 µC **2kΩ** Unknown **10kΩ** Unknown
Max phase charge density (pulse width x peak current) / electrode surface area	**500Ω** 497.63µC/cm^2 – Per Pulse **2kΩ** 497.63µC/cm^2 – Per Pulse **10kΩ** 497.63µC/cm^2 – Per Pulse	**500Ω** Unknown **2kΩ** Unknown **10kΩ** Unknown	**500Ω** Unknown **2kΩ** Unknown **10kΩ** Unknown
Max average power density (Duty cycle x peak current)^2 x	**500Ω,** 0.12mW/cm^2	**500Ω,** Unknown	**500Ω,** Unknown

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(load Ω) ÷ electrode surface area)	**2kΩ** 0.5mW/cm^2 **10kΩ** 2.49mW/cm^2	**2kΩ** 9.19mW/cm^2 **10kΩ** Unknown	**2kΩ** Unknown **10kΩ** Unknown
Electrode number	2 Electrodes	2 Electrodes	2 Electrodes

VII. Performance Data

Non-clinical tests

The Modius Sleep 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 Sleep device has demonstrated compliance to ISO 10993-1: Biological evaluation of medical devices – Guidance	Passed
Electrical Safety	The Modius Sleep device was tested to confirm that it met the applicable standards for electrical safety (IEC 60601-1)	Passed
EMC	The Modius Sleep device was tested to confirm that it met the applicable standards for electromagnetic compatibility (EMC) (IEC 60601-1-2)	Passed
Usability Testing	Modius Sleep 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 Sleep device.	Passed
System Verification and Validation Testing	The system verification and validation testing was performed to verify the hardware and firmware of the Modius Sleep Device	Passed

510(k) Summary

Labeling

The labeling for the device included 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 determine the best treatment settings to use. As such, please see 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 1, 1970 to November 8, 2022)

As of November 2022, there were a total of 23 studies that evaluated the effectiveness of CES on insomnia. Of the 11 randomized control trials (RCT), some reported greater reduction in insomnia symptoms in the CES group compared to placebo[1;2;3;4;5], while others reported no significant differences in measures of insomnia symptoms between the 2 groups[6;7;8;9;10;11] .Among the 8 observational studies, CES treatment was associated with less frequent[12] and less intense[13] sleep disturbances, improved soundness of sleep[14], less difficulty falling asleep[14;15;16] and feeling more rested[15] or improved mood[14] in the morning. Several observational studies reported no impact of CES on insomnia[17;18] or reported an effect that did not persist after the first week[19]. A meta-analysis of 14 RCTs indicated that CES versus sham treatment had no impact on insomnia[20]. Lastly, 3 reviews evaluated the effectiveness of CES on insomnia. One review found 23 studies, 6 of which were RCTs of which only 2 studied participants with insomnia[21]. Of these two RCTs, only 1 showed improved patient-reported sleep latency and objective changes in sleep, while the other did not show any change[21]. The other 2 reviews concluded that studies evaluating the effectiveness of CES on insomnia were inconclusive[22] or inconsistent[23]. In studies that reported improvement in insomnia with use of CES, the reported stimulation parameters, electrode placement, and treatment schedule varied widely and were only evaluated in a small number of combinations.

Please note that not all combinations of parameters provided below have been studied for safety and effectiveness; therefore, individuals using this device should work with the prescribing medical provider to determine the best treatment settings to use and should not apply electrodes to locations that are not indicated in the specific product's labeling. Please

also note that not all CES devices are capable of providing the same stimulation parameters or combination of stimulation parameters.

Please see information below on the 23 studies (January 1, 1970 to November 8, 2022) noted above that evaluated the effectiveness of CES on insomnia:

Electrode placement:

- Over orbits and mastoids
- Over eyelid and mastoids
- Over orbits and occiput
- Earlobes

Waveform:

- Square
- Rectangular, monophasic

Frequency:

- 100 Hz
- 350 Hz
- 0.5 Hz
- 14 Hz

Pulse Width:

- 0.7 ms
- 1 ms
- 2 ms

Maximum current:

- 0.01-1.9mA

Treatment schedule:

- 30 minutes, 5 times a week for 1-2 weeks

- 30-minute sessions twice a day
- single 20-30 minute session
- 15 minutes daily for 24 days
- 30 minutes for 1-7 days

Clinical Testing of Modius Sleep

Clinical testing of Modius Sleep included a pivotal randomized, double blind sham controlled clinical trial to evaluate the safety and efficacy of the Modius Sleep Electrical Vestibular Stimulation (VeNS) device, for the treatment of chronic insomnia.

Study design

A 4-week pivotal randomized controlled trial with two groups 1) Modius Sleep device group and 2) Sham (placebo) control group was used to evaluate the safety and efficacy of the Modius Sleep device as a treatment for chronic insomnia.

The study was a multi-site, randomised, double blinded, sham-controlled trial conducted from May 2022 to January 2023. The study has been registered at https://clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT04452981). Research sites included University of Ulster, United Kingdom (UK), and Hong Kong Polytechnic University, Hong Kong (HK). The study protocol was approved at the UK site by Wales Research Ethics Committee 7 (Ref: 22/WA/0022) and at the HK site by the Human Subjects Ethics Sub-Committee, Hong Kong Polytechnic University (Ref: HSEARS20220320001). Informed consent was obtained from all participants.

Adults with an Insomnia Severity Index (ISI) score of 15 or higher were recruited using online platforms and randomly allocated (1:1 allocation ratio) to receive the Modius Sleep device (intervention group) or the sham device (active control group). Both groups were advised to use their allocated devices for 30 minutes per day prior to going to sleep for a four-week duration. The devices are identical in appearance and therefore neither the participant nor the clinical study team knew whether the Modius Sleep device or sham device was allocated. Primary and secondary outcomes were captured at baseline and at 4 weeks.

126 participants (aged 19-67 years) with moderate to severe insomnia assessed by the insomnia severity index (ISI) were enrolled. While the ISI is a useful screening tool for insomnia, it does not cover all components of The AASM (American Academy of Sleep Medicine) International Classification of Sleep Disorders (ICSD), and The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) that are used for diagnosis of chronic insomnia. For this reason, further information was collected by an online survey to establish that the participants had chronic insomnia at the time of enrolment as defined by ICSD and DSM-V. Specifically, information was collected regarding the duration and frequency of their sleep disturbance and associated daytime symptoms, confirmation of adequate opportunity and conditions to sleep, and confirmation of no other co-existing conditions. This further information provided confirmation that the participants had Chronic Insomnia at the time of enrolment in the Modius Sleep trial.

For the duration of the study, participants agreed not to take prescribed or over the counter sleeping medication; not to undergo any extreme lifestyle changes that could have impacted their sleep quality; not to use sleep trackers; not to travel to different time zones and to maintain a familiar sleeping routine.

Primary Effectiveness Endpoint

The efficacy of the Modius Sleep device was quantified by change in the Insomnia Severity Index (ISI) score[24] at Week 0 and Week 4 between the Modius Sleep group and sham control group.

Primary Safety Endpoint

An evaluation of the safety of the Modius Sleep device was quantified by the occurrence in adverse events between the Modius Sleep group and sham control group.

Results

A total of 149 eligible participants were recruited and randomised to the Modius Sleep group (n=75) or the sham control group (n=74). Twenty-three participants withdrew from the study

before the 4-week visit. A complete case analysis was undertaken on all participants (n=126) with available data at baseline and at the 4-week visit. The mean age of the sample (67% female) was 41 years (age range: 19 to 67 years).

Table 6: Participant accountability

Stage	Modius Sleep Device	Sham control device	Total
Enrollment	75	74	149
Treatment	75	74	149
Primary safety endpoint analysis	75	74	149
Primary effectiveness endpoint analysis	61	65	126
Secondary endpoint analysis	61	65	126

Table 7: The effect of Modius Sleep on Insomnia Severity Index (Primary outcome all participants)

	Modius Sleep	Sham control	Between-group difference mean (95% CI); P value[b]		
	Mean (SD)	Mean (SD)	Model 1	Model 2	Model 3
ITT (MI)					
Baseline	19.77 (0.48)[c]	18.36 (0.52)[c]			
4 weeks	13.99 (0.65)[c]	14.67 (0.78)[c]	-2.08 (-3.93, -0.24) 0.028	-2.13 (-4.34, 0.07) 0.058	-1.93 (-4.02, 0.16) 0.070
Within-group mean change (95% CI); P value[a]	-5.78 (-6.93, -4.63) <0.001	-3.70 (-4.99, -2.41) <0.001			
ITT (LOCF)					
Baseline	19.77 (4.14)	18.36 (4.51)			
4 weeks	14.82 (5.12)	15.22 (6.11)	-1.80 (-3.24, -0.35) 0.015	-1.88 (-3.68, -0.07) 0.042	-1.76 (-3.62, 0.10) 0.064
Within-group mean change (95% CI); P value[a]	-4.95 (-5.90, -3.99) <0.001	-3.15 (-4.25, -2.05) <0.001			
Complete case					
Baseline	19.72 (4.03)	18.34 (4.69)			
4 weeks	13.92 (4.67)	14.82 (6.30)	-2.28 (-3.85, -0.71) 0.005	-2.49 (-4.45, -0.53) 0.013	-2.40 (-4.36, -0.44) 0.017
Within-group mean change (95% CI); P value[a]	-5.80 (-6.79, -4.81) <0.001	-3.52 (-4.74, -2.30) <0.001			

[a]Within-group mean change in ISI scores from baseline to week 4 analysed using paired sample t-test. [b]Between-group difference in ISI scores (dependent variable) from baseline to week 4 analysed using ANCOVA. Model 1 includes treatment group as the independent variable; model 2 includes treatment group, site and treatment group-by-site interaction; and model 3 includes the covariates in model 2 as well as sex (Male vs Female), age continuous, and race (White vs Asian vs Mixed). [c]Standard error in brackets. Intention-to-treat analysis, ITT (Multiple Imputation, MI and Last observation carried forward, LOCF) includes all participants randomised and who had baseline ISI scores (Modius Sleep, n=73 and sham control n=74). Complete case analysis includes participants who had baseline and 4-week ISI scores (Modius Sleep n=61 and sham control n=65).

Outcomes

The effect of the Modius Sleep device on change in ISI score from baseline to the 4-week visit is shown in Table 7 above. The results show that the Modius Sleep group had a greater and statistically significant reduction in ISI score compared with the sham control group.

AE reports were minor and all self- resolving including, headaches, nystagmus (eye movements), low mood, and mild tinnitus. Rate of AE reporting was 12% (9 participants out of 75) in the Modius Sleep group vs 8% (6 participants out of 74) in the Sham group. There were no device related SAE's reported during the study. One non-device related SAE was reported during the study. Further information below.

Effectiveness

The effect of the Modius Sleep device on change in ISI score from baseline to the 4-week visit is shown in Table 7. The ITT (MI and LOCF) and complete case analyses both demonstrated that both randomization groups reduced their ISI scores; however, the Modius Sleep group had a significantly greater reduction in ISI score (model 1). When site and treatment group-by-site interaction were added as covariates (model 2), the greater reduction in ISI score observed in the Modius Sleep group remained significant for the LOCF ITT and complete case analyses and approached statistical significance for the MI ITT analysis. Model 3 included the covariates from model 2 and demographic variables including age, sex, and race. The greater reduction in ISI score observed in the Modius Sleep group remained statistically significant for the complete case analysis and approached statistical significance for both ITT (MI and LOCF) analyses.

Discussion (Effectiveness)

To determine if the treatment effect found in model 1 was homogeneous across the research sites (HK and UK), model 2 additionally included the variables site and treatment-by-site interaction. The statistically significant treatment effect remained for the LOCF ITT and complete case approaches as described above. Furthermore, the treatment-by-site interaction was not significant in the ITT (MI & LOCF) or complete case models, which indicates that the treatment effects can be combined across the sites to create an overall estimate of treatment effect. The treatment effect, however, did not remain significant for the MI ITT approach. This

approach accounts for uncertainty and is less bias than the single imputation method (LOCF); however, it provides the most conservate estimate of treatment effect.

To investigate consistency of the treatment effect across subgroups, model 3 included the covariates sex (Male vs Female), continuous age, and race (White vs Asian vs Mixed). Results showed that the covariates added in the model were not significant in the ITT (MI or LOCF) or complete case models which indicates the treatment effect is consistent across these subgroups. As mentioned above, the statistically significant treatment effect remained for the complete case analysis and only approached statistical significance for both ITT (MI and LOCF) analyses. An ITT analysis includes all the participants who were randomized and analysed according to the treatment group they were assigned. The benefit of this type of analysis is that it produces unbiased estimates of treatment effects, provides the greatest generalisability, and preserves the sample size. The treatment effects, however, are usually conservative because it includes people who have withdrawn from the study and those who did not comply with treatment. The complete case analysis includes participants who completed the study and had data collected at baseline and at the 4 week follow up visit. This type of analysis provides information on how the treatment (Modius Sleep) performs in an ideal situation, i.e., includes only people who adhered to the intervention. The addition of the covariates in model 3 may have also reduced the power to detect a significant treatment effect in the ITT analyses.

Safety

A total of 22 Adverse Events were reported during the 4-week study (16 reported by the Modius Sleep group vs. 6 reported by the sham control group), these included headaches and nausea, which are known side effects of cranial electrical stimulation. One finding of a Serious Adverse Event (minor cerebrovascular accident) was reported during follow up with a participant who had been previously withdrawn. Assessment of the participant by the hospital-based medical team reported previously undiagnosed hypertension (high blood pressure) which is believed to have been the cause of this event, and therefore this was not classified as a device related SAE. The patient's hypertension was subsequently treated with no further events reported.

The adverse events were all minor, caused a minimal discomfort to participants, and all self-resolved during the period of the study. Clinical and research studies report the possibility of mild adverse effects including skin irritation, discomfort from the stimulation, sensation of feeling off-balance, dizziness, nystagmus (eye movements), blurred or flashing vision, headache, nausea, and tinnitus.

Table 8: Number (%) of Adverse Events (Safety Data Analysis) according to Randomisation Group (all participants, n=149)

		Total n (%)	Modius Sleep n (%)	Sham Control n (%)
Nervous System Disorders	Headache/migraine	7 (4.7)	6 (4.0)	1 (0.7)
Eye Disorders	Flashes in peripheral vision	2 (1.3)	2 (1.3)	0 (0)
	Shadow in peripheral vision	1 (0.7)	1 (0.7)	0 (0)
	Tingling in eye	1 (0.7)	1 (0.7)	0 (0)
Ear disorders	Ear pain	2 (1.3)	0 (0)	2 (1.3)
	Tinnitus	2 (1.3)	1 (0.7)	1 (0.7)
	Itching in ear	1 (0.7)	0 (0)	1 (0.7)
Mood disorders	Low Mood	2 (1.3)	2 (1.3)	0 (0)
Mouth/dental disorders	Metal fillings pulsing	1 (0.7)	0 (0)	1 (0.7)
	Grinding teeth	1 (0.7)	1 (0.7)	0 (0)
Gastrointestinal Disorders	Nausea	1 (0.7)	1 (0.7)	0 (0)
Other	Tingling in arm	1 (0.7)	1 (0.7)	0 (0)

Adverse Events are grouped by Body System and Reported Term and sorted by descending frequency of reported event. Includes withdrawals. Participants could have reported more than one event.

The AE's reported in this study are listed in the table above. There was no significant difference between the AE's reported in both groups. All AE's were self-limiting and resolved when the device usage was stopped.

510(k) Summary

The risk of these adverse effects occurring is usually mitigated by reducing or stopping the stimulation. If a user does experience these adverse effects, they should stop stimulation by turning off or removing the device.

The following warnings have been included in the labelling:

- To mitigate the risk of dizziness, the device must be worn when seated, and start stimulation at a low level and increase gradually to the highest comfortable level. If you do experience dizziness, stop stimulation by turning off or removing the device. If dizziness persists, please consult your physician.

- To mitigate the risk of headaches, the device must be worn when seated, and start stimulation at a low level and increase gradually to the highest comfortable level. If you do experience a headache, stop stimulation by turning off or removing the device. If the headache persists, please consult your physician.

- The Modius Sleep device should only be used as prescribed by a trained physician.

Generalizability of study data

The Modius Sleep trial consisted of two clinical sites, with one based in the United Kingdom (UK) and the other in Hong Kong (HK). 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 Sleep study, with two of these populations being recruited nationwide (as opposed to the close proximity of the clinical site).

UK and HK participants met the same definition of insomnia and had the same ISI inclusion criteria of 15 or greater. The baseline ISI scores reported for the Modius Sleep study are in

line with literature, and comparable across the two sites (HK 19.11 and UK 18.82). An Insomnia study involving Hong Kong participants, that utilized the ISI to measure sleep improvement, has reported comparable baseline ISI scores to the US. Yin et al.[25] conducted a randomised controlled trial (RCT) to evaluate the efficacy and safety of acupuncture treatment for primary insomnia. The study enrolled patients from Shanghai Municipal Hospital of Traditional Chinese Medicine, and the primary outcome was change in ISI score, and the intention to treat population demonstrated a baseline ISI score of 17. Ong et al.[26], evaluated the efficacy of mindfulness meditation for the treatment of chronic insomnia recruiting patient from Rush University, US. The average baseline ISI score for the three treatment groups was 16.8. Another trial evaluating mindfulness in Los Angeles reported an average baseline ISI score of 17.8.[27]

Furthermore, a recent population-based survey of adults in Hong Kong estimated the prevalence of insomnia to be 20.7%.[28] This was twofold higher than the insomnia estimate (11.9%) from a 2002 survey, using a comparable measure[29]. Approximately 10% of the adult population suffers from an insomnia disorder and another 20% experiences occasional insomnia symptoms[30]. Data from The National Health Interview Survey reported 14.5% of adults had trouble falling asleep and 17.8% of adults had trouble staying asleep. As such, the prevalence of insomnia in Hong Kong is comparable to both global and US estimates. Additionally, a study comparing the both the prevalence of insomnia according to different diagnostic measures, and between Hong Kong and the United States by adopting a similar methodology used by the America Insomnia Survey (AIS), showed that the prevalence of insomnia disorder was similar for Hong Kong and the United States.[31]

An important consideration regarding generalizability for this body of evidence is that because we were seeking to treat individuals prior to their use of other interventions (e.g., drugs), the remaining potential confounding factor would be if there were differences in the presentation and diagnosis of the disease based on race/ethnicity. We were unable to find any evidence to suggest that such a difference exists. We also note that when verifying the presence of insomnia at each site as described above, the same criteria were used in both cases. Even if

both sites were within either the UK or Hong Kong, it would have been entirely possible for the baseline mean to vary between those two sites and yet not affect overall generalizability.

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 sleep, beta blockers, or who regularly use antihistamines.
- Persons with a history of stroke, or severe injury to the brain.
- Persons with an active significant mental health disorder or cognitive impairment.
- Persons with any disease which may cause vestibular neuropathy.
- Persons with myelodysplastic syndromes, or history of malignancy in the past 12-months.

Conclusion

A complete case analysis of this pivotal study reported that participants using the Modius Sleep device daily demonstrated a statistically significant improvement in their insomnia at 4 weeks.

VIII. Safety and Effectiveness Conclusion

Based on the clinical performance as documented in the pivotal clinical study, Modius Sleep is a low-risk, non-invasive, drug-free therapy, that provides a statistically significant benefit at 4 weeks when used to treat chronic insomnia.

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

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