SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Genio® System for Obstructive Sleep Apnea (OSA)

Device Trade Name: Genio® System 2.1

Device Product Code: MNQ

Applicant's Name and Address: Nyxoah Inc.
251 Little Falls Drive
Wilmington, DE 19808

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P240024

Date of FDA Notice of Approval: 08/08/25

II. INDICATIONS FOR USE

The Genio® System 2.1 is indicated for use in the treatment of moderate to severe Obstructive Sleep Apnea (OSA) (apnea-hypopnea index [AHI] of greater than or equal to 15 and less than or equal to 65). The Genio® System 2.1 is intended for adult patients 22 years of age and older who have been confirmed to fail, cannot tolerate or are ineligible to be treated with current standard of care treatments including lifestyle modifications, positive airway pressure (PAP) treatments (such as continuous positive airway pressure [CPAP] or bi-level positive airway pressure [BiPAP] machines), oral appliances (such as mandibular advancement devices), and pharmacotherapy (such as tirzepatide).

PAP failure is defined as an inability to eliminate OSA (residual AHI of greater than 15 despite PAP usage), and PAP intolerance is defined as:

1. Inability to use PAP (at least 5 nights per week of usage; usage defined as greater than 4 hours of use per night), or

2. Unwillingness to use PAP (PAP therapy initiated and subsequently discontinued by choice).

III. CONTRAINDICATIONS

The Genio® System 2.1 is contraindicated for:

- Patients with combined central and mixed apnea-hypopnea index greater than or equal to 25% of the total AHI.
- Patients with any functional or structural problem, medical illness or condition that would prevent or interfere with implantation, activation or continued use of the Genio therapy.
- Patients with an implantable device which may be susceptible to unintended interaction with the Genio® System. Consult the device manufacturer to assess the possibility of interaction.
- Women who are pregnant, planning to become pregnant or breastfeeding.
- Any condition or procedure that has compromised neurological control of the upper airway.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Genio® System 2.1 labeling.

V. DEVICE DESCRIPTION

The Genio® System 2.1 is a hypoglossal nerve stimulator intended for the treatment of moderate to severe Obstructive Sleep Apnea (OSA). It consists of an Implantable Stimulator (IS) designed to stimulate the hypoglossal nerve (HGN) terminal branches bilaterally (i.e., both the left and the right). The IS does not include a battery or software but receives energy pulses transmitted by either the External Stimulator (ES) during the implantation procedure or the Activation Chip (AC) during therapy which is attached to an adhesive Disposable Patch (DP) and placed on the patient's skin under the chin. The Genio waveform received by the IS is a rectified square wave that allows for passive discharge to achieve charge balanced stimulation pulses which are delivered to the HGN. Stimulation of the HGN causes specific tongue muscles to contract resulting in the forward movement of the tongue which in turn maintains an open airway during the patient's sleep.

During awake or sleep lab titration, the stimulation parameters transmitted by the AC to the IS are programmed using the Sleep Lab Application software which is run on an off-the-shelf mini-computer (Repeater). Once an optimal stimulation amplitude range has been programmed for the AC, a Smartphone Application available on both Android and iOS devices can be used by the patient to pause and resume treatment as well as adjust the stimulation level within a pre-defined safe range. The range is set by the Nyxoah field personnel (Registered Polysomnography Technologist*)* under the directions provided by the physician. The AC is charged daily using a Charging Unit (CU). The Genio® System 2.1 components for patient use are shown in Figure 1 below.

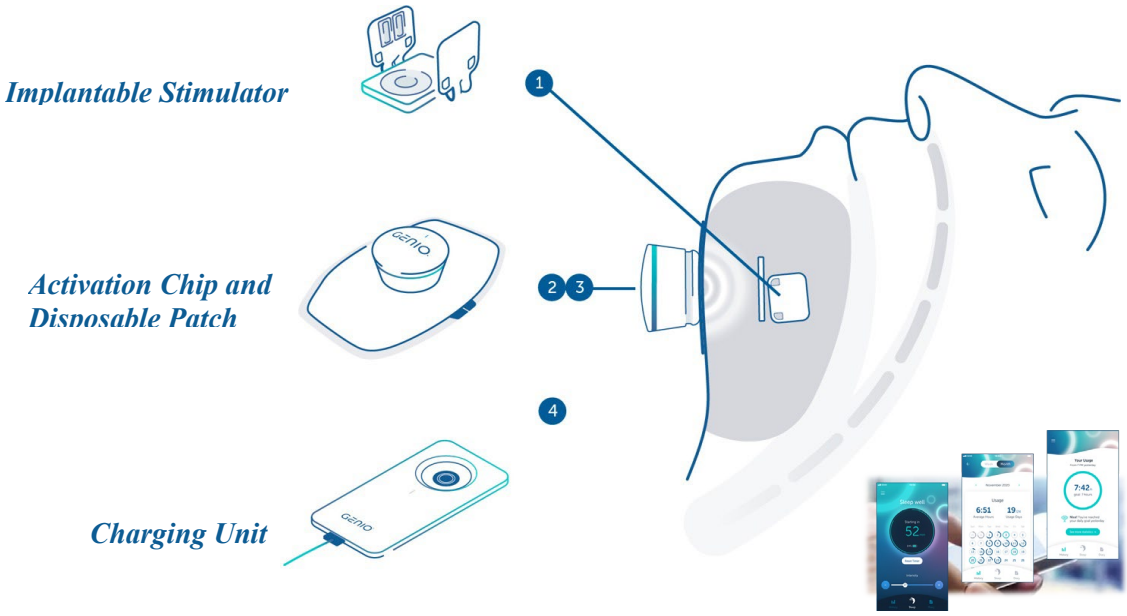

Figure 1. Genio® System 2.1 Components for patient use

A description of the implanted and external components of the Genio® System 2.1 are provided below. Additionally, a summary of the technical specifications for each of the physical Genio® System 2.1 components (i.e., components that are not software) has been provided in Table 1.

Table 1. Technical Specifications of the Genio® System 2.1 Components

Component	Dimensions	Weight	Shelf-life	Service Life
Implantable Stimulator Model #2954	L=27.3mm W=20.7mm H=4.4mm	6.18g	2 years	At least 12 years
Surgical Template	L=27.3mm W=20.7mm H=4.4mm	3.09g	2 years	N/A – single use disposable device
External Stimulator	L=115.15mm W=23.5mm H=33.8mm	28.90g	1 year	N/A – single use disposable device
Disposable Patch (liner included)	L=101mm W=71.7mm H=6.61mm	3.25g	• Sealed bag: Maximum 16 months • Opened bag: 15 days	N/A – single use disposable device

Activation Chip Model #2364	Ø = 31.40mm H=20.55mm	12.18g	1 year	At least 12 months
Charging Unit Model #2238	L=110mm W=50mm H=17mm	61.69g	1 year	At least 12 months

Implantable Stimulator (IS) Model #2954

The IS Model #2954 is a single-use, sterile, small saddle-shaped implant that delivers stimulation to both HGN branches (i.e. left and right). The body of the IS consists of an energy receiving antenna and an electrical circuit both encapsulated in a ceramic housing, and two lateral legs with a pair of paddle electrodes. It is powered and controlled by either the AC or ES externally. The IS does not include a battery or a microcontroller or software. The IS is implanted in a single incision surgical procedure under the chin and placed over the genioglossus muscle with its paddle electrodes facing both left and right HGN branches. The device is sutured in place to the genioglossus muscle using the four IS leg suturing pads. The electrodes conduct stimulation energy to the HGN, resulting in contraction of the tongue muscles. This process can help maintain an open airway and normal breathing during sleep. The IS is the only implantable component of the Genio® System 2.1. An illustration of the anatomical location of the IS once implanted is shown in Figure 2 below.

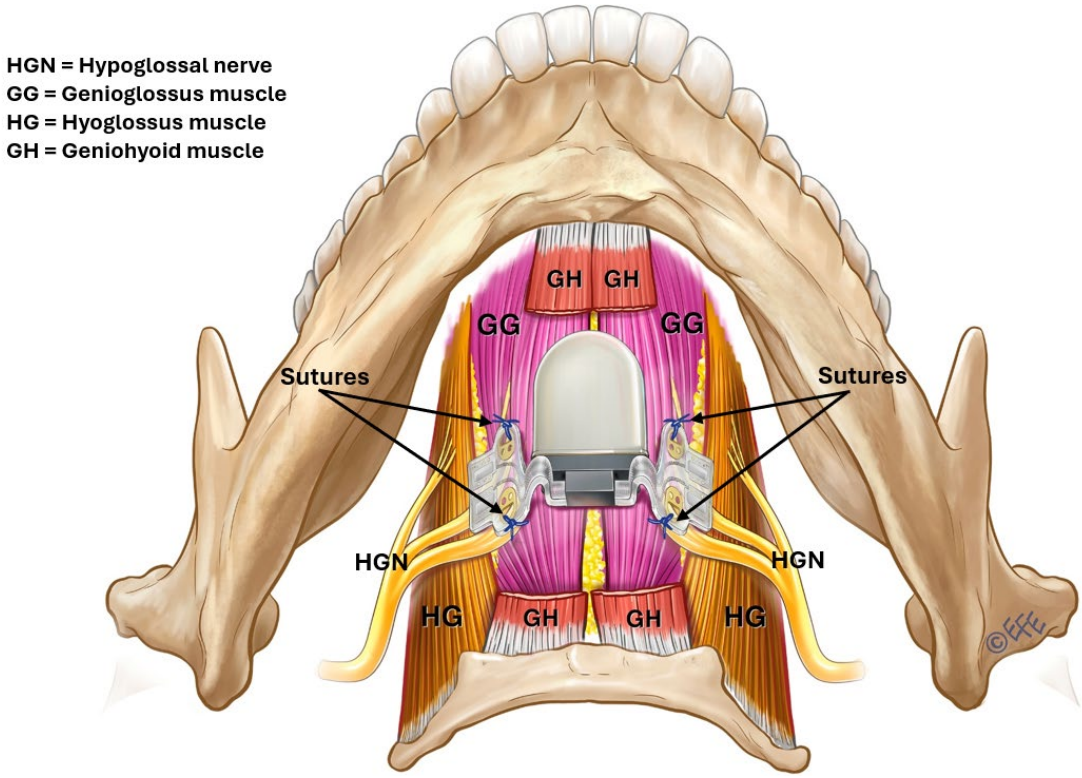

Figure 2. Illustration of Genio® System 2.1 Anatomical Location including Suturing Points

The Genio® Implantable Stimulator Model #2954 (Figure 3) is a Magnetic Resonance (MR) Conditional device which means that the implant is safe in the MR environment within certain conditions.

Figure 3: Implantable Stimulator (IS) Model #2954

Packaged with the IS Model #2954 is the Surgical Template (ST) (Figure 4). The ST is a single use, sterile accessory which can be optionally used for preparation of the implantation site.

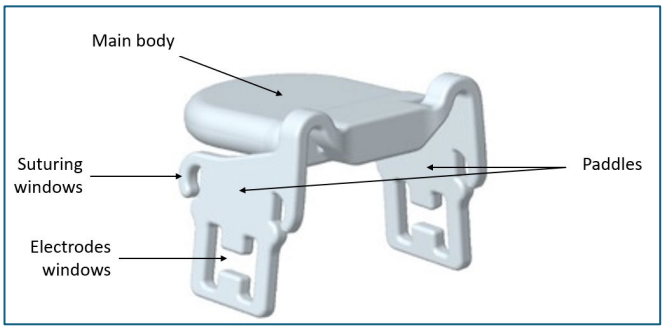

Figure 4: Surgical Template

External Stimulator (ES)

The ES (Figure 5) is a single-use, sterile accessory that allows the surgeon to activate the IS and verify the functionality of the implant during the surgical procedure. The ES contains a power button with an LED indicator, a pre-charged battery and a retractable scaling mechanism to control the stimulation intensity delivered to the implant.

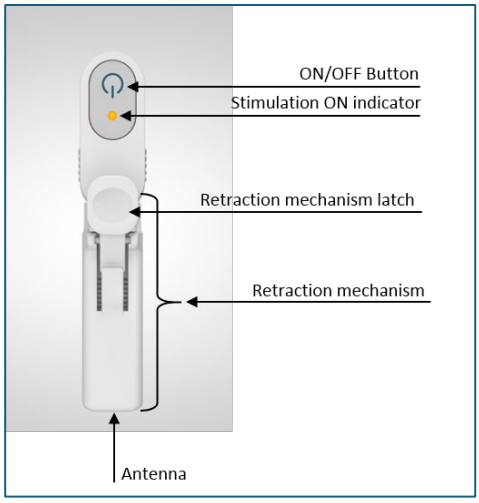

Figure 5. External Stimulator

Disposable Patch (DP)

The DP (Figure 6) is a single-use adhesive patch placed on the skin under the chin each night by the user. The Activation Chip is snapped onto the DP using a button connector. Once snapped together, stimulation energy can be transmitted wirelessly to the IS. The DP is comprised of a flexible Printed Circuit Board (PCB) (the antenna) and an adhesive patch.

Figure 6. Disposable Patch

Activation Chip (AC) Model #2364

The AC (Figure 7) is the power source for the IS. The AC contains a rechargeable battery, electronics for Bluetooth communication and electromagnetic power transmission, and a microprocessor that stores the user-specific stimulation parameters. Nyxoah field personnel (Registered Polysomnography Technologist) program the AC stimulation parameters specific for each user to provide optimal therapy under the guidance of the Health Care Provider (HCP). The AC must be connected to the DP and placed on the chin each night for stimulation to be delivered, and the battery must be recharged daily.

Figure 7. Activation Chip Model #2364

Charging Unit (CU) Model # 2238

The CU (Figure 8) and its power adapter are used to recharge the AC battery during the day in order to be ready for use the following night. The CU is comprised of a docking area to plug the AC in, a power LED indicator and a micro-USB port to connect to the power adapter.

Figure 8. Charging Unit Model # 2238

Sleep Lab Application

The Sleep Lab Application (Figure 9) is used by Nyxoah field personnel to configure the AC stimulation parameters. This remote application runs on a small mini-computer (Repeater) and uses Bluetooth low energy (BLE) protocol to enable the operator to configure/customize the AC stimulation parameters. Once the AC is connected to a DP, the Sleep Lab App can be used to perform AC check-ups, read usage data stored in the AC and program/adjust the stimulation parameters.

Figure 9. Sleep Lab Application

Smartphone Application (optional)

The AC can be controlled by an optional Smartphone Application (Figure 10), designed to operate on both Android and iOS devices which allows the patient to pause and resume stimulation and to increase/decrease the treatment amplitude within a pre-configured range. The Smartphone App uses BLE protocol to communicate with a paired AC.

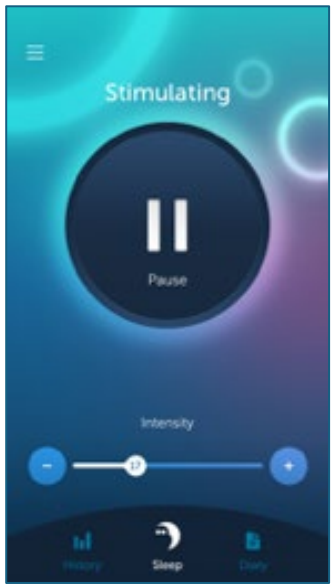

Figure 10. Smartphone Application

Stimulation Parameters

The stimulation parameters are controlled by the AC and configured in the sleep lab using the Sleep Lab App. These parameters include pulse amplitude, frequency, duration as well as stimulation train parameters such as train length (on time) and train interval (off time). The pre-defined range for the stimulation parameters is configured by field personnel (Registered Polysomnography Technologists) in accordance with direction provided by the sleep physician. Using the optional Smartphone App, the patient also has the ability to fine tune the amplitude, within a pre-defined limit. Table 2 below lists the configured stimulation parameters values. All parameters can only be modified by the field personnel except for amplitude which can be fine-tuned by the patient using the optional Smartphone App.

Table 2. Stimulation Parameters Ranges, steps and default values

Treatment Parameter	Description	Available Range (step)	Default Setting
Pulse Length	Duration of one stimulation pulse	50-250 µsec (10µsec)	100 µsec
Pulse Frequency	Pulse repetition rate within stimulation train	30-50 Hz (5Hz)	30 Hz
Train Length	Duration of stimulation train	0.2-5sec (0.1sec)	1 sec
Train Interval	Duration of pause between stimulation trains	0.2-5sec (0.1sec)	4 sec
Treatment Amplitude	Stimulation amplitude	1-100 % (1%)	1%
Lowest Amplitude Limit	Stimulation amplitude bottom limit for Smartphone application	1-100 % (1%)	1%
Highest Amplitude Limit	Stimulation amplitude top limit for Smartphone application	1-100 % (1%)	1%
Delay time	Time between the connection of the AC-DP and the start of the stimulation therapy	5-60 min (5min)	30 min
Ramp Up duration	Time for stimulation amplitude ramp up within train (linear distribution).	0 -1000 msec (50msec)	0 - Not active
Hold Time Duration	Duration time after reaching train amplitude target prior to step-down execution	0 – 500 msec (50msec)	0 - Not active
Step down Target amplitude	Stimulation amplitude step reduction within a pulse	1 - 100% (1%)	0 - Not active
Ramp at stimulation Onset	Time for stimulation amplitude ramp up between trains (linear distribution) during the treatment initiation.	0-30 min (5min)	0 - Not active

The stimulation parameters described in Table 2 above are illustrated in Figure 11 through Figure 13 below. These figures provide a visual representation of the IS stimulation pulses delivered to the HGN when triggered by the radiofrequency (RF) energy sent from the AC. Figure 11 illustrates the train length, train interval, pulse amplitude, pulse frequency and pulse duration stimulation parameters. The amplitude ramp up within each train setting is depicted in Figure 12 while the stimulation ramp up at therapy initiation setting parameters are shown in Figure 13.

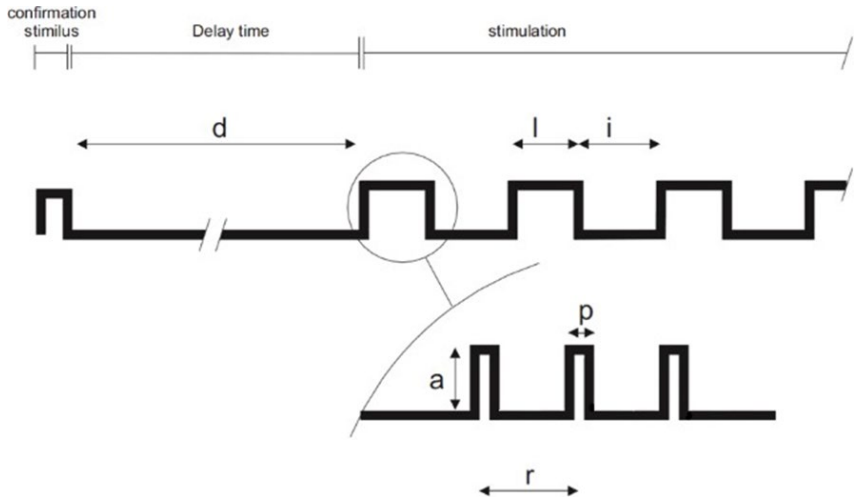

Figure 11. Illustration of Genio® System 2.1 stimulation parameters (l = train length, i = train interval, a = treatment amplitude, r = pulse frequency, p = pulse duration, d = delay time)

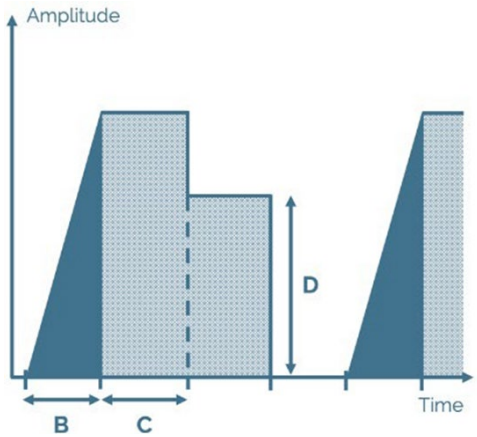

Figure 12. Amplitude ramp up within each train pulse setting parameters (B = ramp up duration, C = hold time duration, D = step down target amplitude)

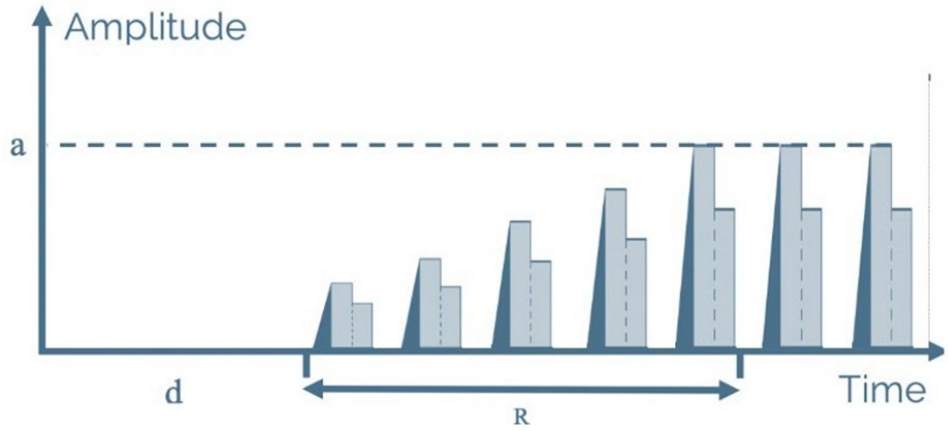

Figure 13. Stimulation ramp-up at the therapy initiation setting parameters (a = treatment amplitude, d = delay time, R = ramp at stimulation onset)

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of obstructive sleep apnea (OSA), including lifestyle changes (e.g., weight loss and positional therapy), PAP (Positive airway pressure), oral appliances (mandibular advancement device), anatomical surgery, and pharmacotherapy (e.g., tirzepatide).

Each alternative has its own advantages and disadvantages. A patient should thoroughly discuss the risks and benefits of treatment alternatives with his/her physician to select the treatment method that best meets their needs.

VII. MARKETING HISTORY

The original Genio® System received CE mark approval on 12 March 2019 under the Active Implantable Medical Devices Directive (AIMDD), while the Genio® System 2.1 was subsequently approved under the Medical Device Regulation (MDR) on 15 July 2022. Both devices have been successfully marketed in the European Union since their respective approvals, with a comparison provided in Table 3. There have been no reports of the Genio® System 2.1 being withdrawn from the European Union market."

The Genio® System 2.1 has not been previously marketed in the United States. Additionally, the Genio® Implantable Stimulator Model #2954 has not received prior marketing approval in any jurisdiction worldwide.

Table 3. Genio® System Comparison

System Component	Genio® System (CE Mark under AIMDD)	Genio® System 2.1 (CE Mark under MDR)	Genio® System 2.1 (PMA P240024)
Implantable Stimulator (IS)	Genio® Implantable Stimulator	Genio® Implantable Stimulator	Genio® Implantable Stimulator Model #2954
External Stimulator (ES)	Genio® External Stimulator	Genio® External Stimulator	Genio® External Stimulator
Disposable Patch (DP)	Genio® Disposable Patch	Genio® Disposable Patch	Genio® Disposable Patch
Activation Chip (AC)	Genio® Activation Chip Model #2218	Genio® Activation Chip Model #2364	Genio® Activation Chip Model #2364
Charging Unit (CU)	Genio® Charging Unit Model # 2219	Genio® Charging Unit Model #2238	Genio® Charging Unit Model #2238
Sleep Lab Applications	Genio® Sleep Lab Application	Genio® Sleep Lab Application (updated)	Genio® Sleep Lab Application (updated)
Bluetooth Snap Device (BTSD)	Genio® Bluetooth Snap Device	N/A (obsoleted)	N/A
Smartphone Application (optional)	N/A	Genio® Smartphone Application	Genio® Smartphone Application

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Temporary local skin irritation
- Impaired or painful swallowing due to the device
- Discomfort or pain due to electrical stimulation
- Mouth blisters (due to tongue rubbing against teeth during stimulation)
- Mild to moderate pain, swelling, stiffness or tenderness at the implant site or with the use of the device
- Mild tongue abrasion
- Abnormal scarring
- Tongue fasciculations (twitching of tongue)
- Dry mouth
- Temporary tongue muscle weakness or soreness
- Temporary usability or functionality issues with an external device leading to temporary delay of treatment
- Permanent usability or functionality issues with an external device leading to no therapy
- Usability or functionality issues with the implanted device

- Increased or continued snoring
- Headache or dizziness
- Fatigue or sleep disturbances, while acclimating to stimulation
- Change in salivary flow
- Clinically significant implant migration (device moving from implanted location and potential partial or complete expulsion of the device from its intended place)
- Impaired sense of taste or metallic taste
- Increased acid reflux
- Increased upper airway secretions
- Paresthesia (sensation of tickling or itching)
- Pain or irritation in the throat or nasal passage
- Allergic and/or rejection response to the implanted device
- Damage to tissue (nerves, blood vessels or muscles) in contact with the implant or in the vicinity of the implant
- Damage to tissue in contact with external devices
- Persistent pain at the implant site
- Impaired or painful speaking due to the device
- Risks related to additional surgery and any unstudied potential effect
- Infection
- Hematoma
- Bleeding
- Cellulitis at surgical site
- Presence of fibrosis making the removal of the Genio® Implantable Stimulator Model #2954 difficult without damaging the surrounding structures

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

Nonclinical testing for the Genio® System 2.1 encompassed a range of evaluations, including bench testing of the device, software and cybersecurity assessments, biocompatibility, sterilization, packaging, shelf-life, MRI safety, electrical safety, electromagnetic compatibility, mechanical/structural durability, human factors, and animal studies. These tests were conducted in accordance with design specifications, as well as relevant standards and guidance documents. A summary of the results for each test is provided below.

A. Biocompatibility

A biocompatibility evaluation was conducted for the Genio® System 2.1 devices in accordance with ISO 10993-1 and its associated standards. The evaluation concluded that none of the Genio® System 2.1 devices contained material which poses a biocompatibility risk to the user. A summary of the Genio® System 2.1 biocompatibility evaluation is provided in Table 4.

Table 4. Summary of the Genio® System 2.1 Biocompatibility Evaluation

Test	Device	Purpose	Result
Cytotoxicity *ISO 10993-5:2009*	Implantable Stimulator Model #2954	Evaluate the Genio® System 2.1 for potential cytotoxic effects.	Pass; non-cytotoxic
	Surgical Template		
	External Stimulator		
	Disposable Patch		
	Activation Chip Model #2364		
	Charging Unit Model #2238		
Sensitization *ISO 10993-10:2010*	Implantable Stimulator Model #2954	Evaluate the Genio® System 2.1 for the potential to cause delayed dermal contact sensitization.	Pass; non-sensitizer
	Surgical Template		
	External Stimulator		
	Disposable Patch		
	Activation Chip Model #2364		
	Charging Unit Model #2238		
Irritation/ Intracutaneous Reactivity *ISO 10993-10:2021*	Implantable Stimulator Model #2954	Evaluate the Genio® System 2.1 for the potential to cause local dermal irritation.	Pass; non-irritating **Note**: There were no gaps between the 2010 and 2021 version of the standard which would necessitate additional testing for these components.
	Surgical Template		
Irritation/ Intracutaneous Reactivity *ISO 10993-10:2010*	External Stimulator		
	Disposable Patch		
	Activation Chip Model #2364		
	Charging Unit Model #2238		

Test	Device	Purpose	Result
Implantation/ Subchronic Toxicity *ISO 10993-11:2017* *ISO 10993-6:2016*	Implantable Stimulator Model #2954	Assess the local and systemic effects of the IS Model #2954 following 13 weeks intramuscular implantation.	Pass; no microscopic evidence of cytotoxicity was observed. Macroscopic gross tissue examination of the implant sites revealed no abnormalities for the test article. The test article showed no local or systemic signs of toxicity when implanted in rabbits for up to 90 days. Additionally, no clinically significant differences were noted in hematology, serum chemistry, or coagulation parameters. No systemic toxic effects were observed.
Genotoxicity *ISO 10993-3:2014*	Implantable Stimulator Model #2954	Evaluate the IS Model #2954 for mutagenic potential and carcinogenic hazards.	Pass; non-genotoxic and non-mutagenic
Material-Mediated Pyrogenicity *ISO 10993-11:2017*	Implantable Stimulator Model #2954 External Stimulator Surgical Template	Determine whether the IS Model #2954, External Stimulator and Surgical Template induce a pyrogenic response.	Pass; non-pyrogenic
Acute Systemic Toxicity *ISO 10993-11:2017*	Implantable Stimulator Model #2954 External Stimulator Surgical Template	Determine whether the IS Model #2954, External Stimulator and Surgical Template induce systemic toxicity from an acute exposure.	Pass; systemically non-toxic
Chemical Characterization *ISO 10993-18:2020*	Implantable Stimulator Model #2954 Surgical Template	Chemical characterization of volatile organic compounds, semi-volatile organic compounds, non-volatile organic	The risk assessment of extractables suggests that the use of the IS Model #2954 or Surgical Template will not present a

Test	Device	Purpose	Result
Toxicological Evaluation *ISO 10993-17:2023*	Implantable Stimulator Model #2954	compounds, and toxicological risk assessment were performed to evaluate the endpoints of chronic systemic toxicity and carcinogenicity for IS Model #2954 and Surgical Template.	significant toxicological or biocompatibility risk.
Toxicological Evaluation *ISO 10993-17:2002*	Surgical Template		

B. Bench Testing

Bench testing of the Genio® System 2.1 devices were conducted to confirm compliance with applicable design requirements and standards. A summary of the test, purpose, acceptance criteria and results for each bench test are provided in Table 5 through Table 10.

Table 5. Summary of Bench Testing Performed on the IS Model #2954

Test	Test Purpose	Acceptance Criteria	Result
Hermeticity Test	Verify that the encapsulation hermeticity adequately protects the electrical circuit from ingress of fluids which may impact the performance or functionality during the device lifetime and that the encapsulation provides protection from release of internal material to the physiological environment	The maximum allowed leak rate of the IS Model #2954 shall be less than: $5 \times 10^{-9} \frac{Pa*m^3}{s}$	Pass
Residual Gas Analysis (RGA) Test	Show that the process used to evacuate dry air (Bake-Out and Helium Backfilling) prior to making the hermetic seal of the implant is effective	The moisture content of the implant shall be ≤ 5,000ppmv (0.5% v/V)	Pass
Dimensions and Weight Test	Ensure compliance with dimensional design requirements	The fully assembled IS shall meet predetermined physical dimensions and weight: - Length: 27mm +0mm/-0.5mm - Width: ≤ 23mm - Height (thickness): ≤ 5.0mm- - Weight ≤ 10g	Pass

Test	Test Purpose	Acceptance Criteria	Result
Fatigue Test	Ensure that the functionality of the IS Model #2954 would not be affected by the mechanical and environmental conditions which would be encountered inside the body during the device's lifetime (12 years)	The tested units shall meet the visual and electrical acceptance criteria after at least 162 million mechanical cycles in the test apparatus	Pass
Shock and Vibration Test	Show that the assembly can withstand mechanical stresses without degradation to its functionality or performance as required by *ISO 14708-1:2014 §23.2 and §23.7*	The IS Model #2954 shall be functional after exposure to mechanical forces and shocks, and meet both visual and electrical functional inspections	Pass
High/Low Pressure Test	Ensure that the implant, when packed in its final packaging, remained fully functional and safe to use when exposed to high and low pressures per *ISO 14708-1:2014 §25.1*	The tested units shall be functional after exposure to high [150 ± 7.5 kPa] and low [70 ± 3.5 kPa] pressure changes -by meeting visual and electrical functional inspection criteria	Pass
Temperature Changes Test	Ensure that the device remains functional and safe for use when exposed to temperatures which may be encountered during storage or transportation per *ISO 14708-1:2014 §26.2*	After exposure to high [55°C ± 2°C] and low [-10°C ± 3°C] temperatures and temperature cycling, the IS Model #2954 shall meet visual and electrical functional inspection criteria	Pass
Mechanical Strength Test	Confirm that the mechanical integrity of the implant is retained after it is subjected to the forces and/or displacements which may be inflicted on the device by the Genioglossus muscle or during handles of the device	The IS Model #2954 functionality shall not be affected by mechanical forces; all electrical parameters measurements shall meet specifications and no visual changes shall occur as a result of exposure to mechanical forces	Pass
Water Ingress Test	Ensure that no fluid ingress occurs in order to guarantee safe use and proper functioning of the implant	The implant shall operate and perform as intended, i.e. - shall meet predefined electrical performance criteria. The implant shall not show visible change in appearance or damage to the silicone coverage or electrodes.	Pass

Test	Test Purpose	Acceptance Criteria	Result
		The implant shall pass RGA test and moisture content shall be ≤ 5000ppmv (0.5%v/v) after the test.	

Test	Test Purpose	Acceptance Criteria*	Result
Finite Element Analysis	To determine forces acting on each individual suture under small static displacement of implant (< 2.5 mm)	Anterior suture • < 0.24 N in Anteroposterior direction • < 0.11 N in Craniocaudal direction Posterior suture • <0.2 N in Anteroposterior direction • <0.22 N in Craniocaudal direction	Pass
Tensile Tests- Implant fixed on a rigid testing fixture	To determine forces exerted on implant's shoulders under large displacement of implant (up to 10 mm)	< 6 N in Anteroposterior direction < 14 N in Craniocaudal direction	Pass
Tensile Tests (in-vitro) - Implant sutured on animal tissue	To determine forces exerted on implant's shoulders under large displacement of implant (up to 20 mm)	Intact system • < 2.7 N in Anteroposterior direction • < 1.6 N in Craniocaudal direction System with one compromised suture • <1.3 N in Anteroposterior direction • <0.65 N in Craniocaudal direction	Pass
	To determine the required displacement of implant to cause suture pull-out	One suture pull-out • < 37 mm in Anteroposterior direction • < 53 mm in Craniocaudal direction Two sutures pull-out • <48 mm in Anteroposterior direction • <63 mm in Craniocaudal direction	Pass

* Acceptance criteria were established based on test results of a previous version of IS.

Table 6. Summary of Bench Testing Performed on the External Stimulator (ES)

Test	Test Purpose	Acceptance Criteria	Result
Retraction Mechanism Test	Ensure that the ES retractor movement's protection prevents unintended movement of the retractor as a result of applied force	The ES retractor protection mechanism shall prevent movement while pressed up to a force of 2Kgf (~20N)	Pass
Power Button Durability Test	Demonstrate that the ON/OFF button is able to withstand the forces applied by the surgeon during the implantation procedure without any failure to device performance	The ES functionality shall not be affected by mechanical forces, i.e. – the ES shall meet predefined electrical performance criteria.	Pass
Operational Battery Lifetime Test	Show there is no performance degradation of the device during low battery conditions and that the battery lifetime meets the design requirements	The operational lifetime of the ES shall be at least 60 minutes	Pass
Performance in Operational Temperature and Humidity Test	Confirm that the ES performance remains optimal at operational temperature and humidity boundary conditions	The ES shall meet predefined electrical performance criteria while exposed to operational temperature [15°C –35°C] and humidity [85% RH] conditions	Pass
Physical Parameters Test	Confirm that the weight of the device is within the range specified in the design requirements	The total weight of the ES shall be < 50g	Pass
Performance in Presence of Metal Retractor Test	Ensure the performance of the ES is not impacted due to the presence of a metal retraction surgery tool	The ES performance shall not be affected by more than ±5% due to the presence of a metal retraction surgery tool	Pass

Table 7. Summary of Bench Testing Performed on the Disposable Patch (DP)

Test	Test Purpose	Acceptance Criteria	Result
Adhesion Integrity	Evaluate the adhesion integrity of the device	The detachment force shall be > 5N	Pass
Bending Durability Test	Ensure that the DP is able to retain mechanical integrity and durability when exposed to bending forces which may be encountered during typical use	Following bending durability testing, the DP shall meet predefined electrical performance criteria	Pass

Test	Test Purpose	Acceptance Criteria	Result
Physical Parameters Test	Ensure that the physical dimensions of the DP fit the anatomical variability which would be encountered during normal use	The fully assembled DP shall meet predetermined physical dimensions: - Length: ≤ 56mm - Width: 74mm – 95mm	Pass

Table 8. Summary of Bench Testing Performed on the Activation Chip (AC) Model #2364

Test	Test Purpose	Acceptance Criteria	Result
Physical Parameters	Ensure the device complies with its relevant design requirements	The fully assembled AC Model #2364 shall meet predetermined physical dimensions: - Height: < 23mm - Diameter: < 33mm	Pass
Storage Conditions Test	Confirm that the device remains fully functional and safe for use when stored at predefined temperature and humidity conditions	Following exposure to storage conditions of temperature [5°C – 40°C] and humidity [up to 85%], the AC Model #2364 shall meet visual and electrical performance criteria.	Pass
LED Visibility Test	Verify the presence of LED visibility for all applicable modes (red, yellow and green)	LED indication shall be visible in an indoor ambient lighting environment at an angle of up to 70° and a distance of up to 1m	Pass
Stimulation Treatment Test	Confirm that the AC interacts as required upon connection/ disconnection from the DP, drives a stimulation pulse through the DP with the configurable set of parameters determined using the Sleep Lab App, and is able to produce a pulse with sufficient charge and peak current values	The AC Model #2364 shall meet the predetermined acceptance criteria for each type of AC stimulation test: AC/DP electrical interface, AC stimulation parameters, and system performance	Pass
Battery Functionality Test	Confirm that the AC battery is able to: power the AC, be recharged, fully charge in less than four hours, and meet certain performance criteria during an operational lifetime of at least eight hours between charges	• A depleted AC battery shall be fully charged in less than four hours. • The AC shall have an operational lifetime of at least eight hours between charges with predefined stimulation parameters and conditions.	Pass

Test	Test Purpose	Acceptance Criteria	Result
Bluetooth Low Energy (BLE) Communication Test	Ensure the AC Bluetooth low energy (BLE) interface enables the device to communicate with a paired device at a distance of up to five meters and that the AC sends an acknowledgement message to the transmitting device upon receiving a message from a paired device over the BLE interface	• The AC Model #2364 BLE interface shall enable the AC to communicate with a paired device located in a distance of up to five meters. Communication is verified based on reading and writing transactions. • The AC Model #2364 BLE connection shall achieve a 95% success rate for 100 "Read Genio® AC" or "Stop Stimulation" transmissions, allowing up to five non-consecutive transmission errors for each set of communication transactions (reading or programming).	Pass
Sensors Functionality Test	Ensure that the sensors of the device will record data upon receiving a command from a paired device and send the paired device this date over BLE.	The Sleep Lab App shall save a file with the sensor's Raw Data sent by the AC Model #2364 over BLE connection in the Repeater	Pass
Weight Test	Confirm that the weight of the device is in compliance with the established design requirements	The AC Model #2364 shall weigh < 90g	Pass
Vibration Durability Test	Show compliance with *ISO 14708-1:2014*	All tested devices shall meet visual and functionality requirements prior to and post vibration	Pass
Performance in Operational Temperature and Humidity Test	Ensure that the device remains fully functional and safe for use within the defined operational temperature and humidity conditions	The AC Model #2364 shall pass predefined electrical performance and visual criteria while exposed to operational temperature [15°C - 35°C] and humidity [85% RH] conditions	Pass

Table 9. Summary of Bench Testing Performed on the CU Model #2238

Test	Test Purpose	Acceptance Criteria	Result
LED Visibility Test	Ensure that the LED of the CU Model #2238 is visible to allow the user to confirm	The CU Model #2238 LED indication shall be visible in an indoor ambient lighting	Pass

Test	Test Purpose	Acceptance Criteria	Result
	proper connection to a power source	environment at an angle of up to 70° and a distance of up to 1m	
Drop Test	Verify the durability of the CU Model #2238 to repeated free falls over the lifetime of the device	The CU Model #2238 shall pass visual, electrical and electrical interface criteria after 12 falls from a height of 80cm on a laminated surface	Pass
Performance and Functionality Test	Confirm that applicable performance and functionality related requirements are met	The CU Model #2238 shall • Have an output voltage of 5±0.25V while connected to the power outlet • Be able to provide an output current of 220mA while connected to the power outlet • Initiate a reset process int eh AC after detachment of the AC from the CU	Pass
Storage Conditions	Confirm that the device remains fully functional and safe for use when stored at predefined temperature and humidity conditions	Following exposure to the defined environmental conditions [5°C – 40°C, up to 85% RH], the CU Model #2238 shall meet visual and functionality test requirements	Pass
Weight Test	Confirm that the weight of the device is in compliance with the established design requirements	The CU Model #2238 shall weigh > 50g	Pass
Vibration Durability Test	Show compliance with *ISO 14708-1:2014*	All tested devices shall meet visual, mechanical and electrical inspections	Pass
Performance in Operational Temperature and Humidity Test	Ensure that the device remains fully functional and safe for use within the defined operational temperature and humidity conditions	The CU Model #2238 shall meet predefined electrical functionality and electrical interface tests criteria while exposed to operational temperature [15°C - 35°C] and humidity [85% RH] conditions	Pass

Table 10. Summary of Device Interface Bench Testing

Test	Test Purpose	Acceptance Criteria	Result
AC/DP Contact Resistance Test	Ensure that when attached to the DP, the interface allows for an efficient transmission of electromagnetic energy between the two devices	All of the AC/DP interface measurements shall have an electrical contact with I resistance of < 0.2Ω at 1.5A DC	Pass

Test	Test Purpose	Acceptance Criteria	Result
Mechanical Interface of the AC/DP Test	Ensure that the devices are fully functional for a lifetime period of one year and that the mechanical performance of each device is within the defined ranges	The AC shall comply with predefined criteria related to AC-DP mechanical durability (attachment-detachment cycles) and the AC-DP mechanical interface (removal, connection and shear force).	Pass
Mechanical Interface of the AC/CU Test	Ensure that the devices are fully functional for a lifetime period of one year and that the mechanical performance of each device is within the defined ranges	The CU shall comply with predefined criteria related to AC-CU mechanical durability (attachment-detachment cycles) and AC-CU mechanical interface (connection and connection durability).	Pass

C. EMC and Electrical Safety Testing

The Genio® System 2.1 was evaluated for EMC and electrical safety testing in accordance with the IEC 60601 standards. A summary of the standards to which each Genio® System 2.1 device complies is provided in Table 11.

Table 11. Summary of Genio® System 2.1 EMC and Electrical Safety Testing

Test	Test Purpose	Acceptance Criteria	Device	Result
Electromagnetic Compatibility (EMC)/Immunity Testing	Verify the device meets international standard for electromagnetic compatibility	IEC 60601-1-2:2014	IS Model #2954	Pass
			ES	
			DP	
			AC Model #2364	
			CU Model #2238	
Electromagnetic Interference (including Wireless Coexistence)	Verify that the device maintains its intended use and does not result in an unacceptable risk due to susceptibility to electrical influences from external electromagnetic fields, including Radio Frequency (RF) signals.	ISO 14708-3:2017	IS Model #2954	Pass
		IEEE/ANSI C63.27:2017	IS Model #2954	Pass
			DP	
			AC Model #2364	
			CU Model #2238	
			Repeater	
		RTCA DO-160G	IS Model #2954	Pass
			AC Model #2364	
		AIM7351731:2021	IS Model #2954	Pass

Test	Test Purpose	Acceptance Criteria	Device	Result
			ES	
			AC Model #2364	
Electrical Safety	Verify the device meets international standards for electrical safety	IEC 60601-1:2005/AMD1:2012	IS Model #2954	Pass
			ES	
			DP	
			AC Model #2364	
			CU Model #2954	Pass
		IEC 60601-1-11:2015	DP	
			AC Model #2364	
			CU Model #2238	
		IEC 60601-2-10:2016	IS Model #2954	Pass
			ES	
			AC Model #2364	
			CU Model #2238	
		ISO 14708-1:2014 ISO 14708-3:2017	IS Model #2954	Pass

D. MRI Safety Evaluation

The implantable component of the Genio® System 2.1 (IS Model #2954) was evaluated in accordance with *ISO/TS 10974:2018 - Assessment of the safety of magnetic resonance imaging for patients with an active implantable medical device* and standard test methods and found to be MR Conditional. A summary of MRI testing conducted on the IS Model #2954 is provided in Table 12.

Table 12. Summary of MRI Testing – IS Model #2954

Hazard	Test Method/Standard	Acceptance Criteria	Results
Magnetically induced displacement force	Measurement of B_0 induced force applied on the implant [ASTM F2052-15]	A deflection angle of < 45°. In case the deflection angle exceeds 45°, a rationale can be provided considering a counter force applied by the sutures with a safety factor of 2	Pass α=1.0°

Hazard	Test Method/Standard	Acceptance Criteria	Results
Magnetically induced torque	Measurement of B_0 induced torque applied on the implant [ASTM F2213-17]	Maximum magnetically induced torque < worst-case gravity torque of the test object (~1.63mNm)	Pass τ_{max}=165.49μNm
Gradient induced vibration (malfunction)	Exposure of the implant to a set of gradient intensive clinical Echo Planar Imaging (EPI) sequences for a total scanning time of 2.5hrs to investigate device damage or malfunction caused by gradient induced vibration [ISO/TS 10974:2018 §10]	The implant shall not suffer from loss of functionality or reduction in performance following the combined exposure to the switched gradient and static magnetic field	Pass; no device damage or performance degradation was detected after exposure
Device malfunction	B_0 induced malfunction: exposure of the device to the static magnetic field in three orientations followed by a full functionality test [ISO/TS 10974:2018 §14]	The implant shall not suffer from loss of functionality or reduction in performance following exposure to the static magnetic field	Pass; no device damage or performance degradation was detected after exposure
Device malfunction	Gradient induced malfunction: measurement of gradient induced malfunction of the implant due to the gradient magnetic field of an MR scanner using a radiated test method and injected test method [ISO/TS 10974:2018 §16]	The implant shall not suffer from loss of functionality or reduction in performance following the exposure to the switched gradient field	Pass; no device damage or performance degradation was detected after exposure

Hazard	Test Method/Standard	Acceptance Criteria	Results
	RF induced malfunction: exposure of the device to radiated RF signals of 64MHz and 128MHz followed by a functionality test of the tested device [ISO/TS 10974:2018 §15]	The implant shall not suffer from loss of functionality or reduction in performance following exposure to the RF fields	Pass; no device damage or performance degradation was detected after exposure
	Combined fields test 1.5T: exposure of the implant to a combination of the three EM fields (static magnetic B_0, switching gradient magnetic field dB/dt, RF field) of the MR system (1.5T) in order to evaluate its robustness against the resulting EM interferences followed by a functionality test of the device [ISO/TS 10974:2018 §17]	The implant shall not suffer from loss of functionality or reduction in performance following exposure to the three EM fields	Pass; no device damage or performance degradation was detected after combined field exposure
Device malfunction	Combined fields test 3T: exposure of the implant to a combination of the three EM fields (static magnetic B_0, switching gradient magnetic field dB/dt, RF field) of the MR system (3T) in order to evaluate its robustness against the resulting EM interferences followed by a functionality test of the device [ISO/TS 10974:2018 §17]	The implant shall not suffer from loss of functionality or reduction in performance following exposure to the three EM fields	Pass; no device damage or performance degradation was detected after combined field exposure

Hazard	Test Method/Standard	Acceptance Criteria	Results
Gradient induced heat	Exposure of the implant to a known switched gradient magnetic field while simultaneously measuring the temperature at different locations near the surface. The test device will be placed in the worst-case orientations to the magnetic flux vector of the pulsed magnetic field simulator [ISO/TS 10974:2018 §9]	The gradient-induced heating Δ of temperature compared to the initial test temperature after an exposure of 30 minutes is below or equal to 2°C, or a CEM43 threshold of 40 is reached (ISO 14708-3:2017 §17)	Pass ΔT=0.2°C for $34.6dB/dt_{rms}$ ΔT=0.6°C for $42.0dB/dt_{rms}$
RF induced heating	An estimate maximum power position around the implant and its hot spots is determined and EM modeling is used to determine the electrical field in the implant volume. The RF power deposition is determined according to the Tier 2 approach [ISO/TS 10974:2018 §8]	The 60 minute temperature rise is below or equal to 6°C	Pass 5.9°C for 1.5T 5.9°C for 3T
Unintended stimulation	Gradient induced lead voltage: injection of induced voltage to an IS electrical circuit and measurement of the output signal of the implant (including Leakage Test and Gradient Rectified Test) [ISO/TS 10974:2018 §13]	– Shannon factor < 1.7 – Charge injection density < $50\mu C/cm^2$ – DC current < $75\mu A/cm^2$	Pass Test Case 1: Leakage test=7.86nC Rectified test=23.6µA Test Case 2: Leakage test 0.2ms=37.8±4.8nC 1.0ms=6.9±0.9nC Rectified test (0.2ms)=0.84±0.10µA

Hazard	Test Method/Standard	Acceptance Criteria	Results
Unintended stimulation	RF induced voltages/RF rectification: injection of RF signals into the IS electrical circuit in order to measure the rectified current and induced voltages resulting from this exposure. A numerical model representing the IS in its nominal production configuration is used for definition of input parameters [ISO/TS 10974:2018 §15]	– Shannon factor < 1.7 – Charge injection density < 50μC/cm^2 – DC current < 75μA/cm^2	Pass; 64MHz – 860.1nC (net charge of 24.1nC) 128MHz – 62.97nC (net charge of 1.89nC)
Image artifact	Measurement of MR image artifacts of the IS due to influences of the field lines of the magnetic field of an MR scanner by the implant [ASTM F2119-07(2013)]	Characterization test only, no pass/fail criteria	N/A; for characterization purposes only

E. Software and Cybersecurity

The Genio® System 2.1 devices which utilize software (AC Model #2364, ES, Repeater with Sleep Lab Application and the Smartphone Application) comply with *IEC 62304:2015 – Medical device software – Software life cycle* processes and any applicable cybersecurity requirements.

The device conformed to the following FDA guidance documents:

- Content of Premarket Submissions for Device Software Functions: June 2023
- Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions: September 2023

F. Packaging and Shelf-Life

The shelf-life for all Genio® System 2.1 devices was established based on various evaluations. Testing for sterile devices were conducted in accordance with *ISO 11607-1:2019 – Packaging for terminally sterilized medical devices – Part 1 : Requirements for materials, sterile barrier systems and packaging systems* and *ISO 11607-2:2019 – Packaging for terminally sterilized medical devices – Part 2 : Validation requirements for forming, sealing and assembly process* standards. Information on the shelf-life for the Genio® System 2.1 devices is detailed in Table 13 below.

Table 13. Summary of Genio® System 2.1 Shelf-Life and Sterility

Device	Sterile/Non-Sterile	Shelf-Life
Implantable Stimulator Model #2954	Sterile	2 years
External Stimulator	Sterile	1 year
Disposable Patch	Non-Sterile	16 months (sealed bag) 15 days (opened bag)
AC Model #2364	Non-Sterile	1 year
CU Model #2238	Non-Sterile	1 year

G. Sterilization

All sterile products of the Genio® System 2.1 (IS, IS Model #2954 and ES) are sterilized using Ethylene Oxide (EO) and have a sterility assurance level (SAL) of at least $10^{-6}$and complies with the requirements of *ISO 11135:2014 – Sterilization of health care products – Ethylene oxide – Requirements for development, validation and routine control of a sterilization process for medical devices*.

H. Human Factors

Human factors validation testing was completed for the Genio® System 2.1 per FDA's 2016 Guidance – *Applying Human Factors and Usability Engineering to Medical Devices* and in accordance with *IEC 62366-1:2015_AMD1:2020 – Medical Devices – Part 1: Application of usability engineering to medical devices*. Human factors validation was performed to demonstrate that the user interface for the Genio® System 2.1 has been designed such that any use errors that could result in harm or impact treatment have been eliminated or reduced as far as possible. Results of the human factor validation tests demonstrated that Genio® System 2.1 can be used by the intended users without serious use errors or problems, for the intended uses and under the expected use conditions. An overview of the Genio® System 2.1 the human factors validation tests are provided in Table 14.

Table 14. Overview of Genio® System 2.1 Human Factors Validation Tests

Intended User	Purpose of Evaluation	Method of Evaluation	Device(s) Evaluated
Patient/Home User	Evaluate user performance based critical tasks related to daily use of the Genio® System 2.1 (e.g., DP placement, use of Smartphone App)	Simulated Use	- AC Model #2364 - DP - CU Model #2238 - Smartphone App
	Evaluate user understanding of critical tasks which could not be observed during simulated use (e.g., warnings, precautions)	Knowledge Questions	
Surgeon	Evaluate user performance based critical tasks related to the implantation procedure specific to human anatomy (e.g., implant placement, suturing)	Simulated Use – Cadaver	- IS Model #2954 - ST
	Evaluate user performance based critical tasks related to the implantation procedure which require in vivo assessment (e.g., verification of implant placement)	Simulated Use – Animal	- IS Model #2954 - ES - AC Model #2364/DP
	Evaluate user understanding of critical tasks which could not be observed during simulated use (e.g., contraindications, warnings)	Knowledge Questions	- IS Model #2954 - ST - ES - AC Model #2364/DP

I. Animal Studies

Acute and chronic animal studies were conducted on swine animal model to evaluate the safety and performance of the Genio® System 2.1 prior to initiating clinical studies. Both studies were performed in compliance with 21 CFR 58 – Good Laboratory Practice for Nonclinical Laboratory Studies. A summary for each of these animal studies is provided in Table 15

Table 15. Summary of Genio® System 2.1 Animal Studies

Study Type	Study Purpose	Study Sample Size	Results
Acute Implantation Studies	Assess feasibility of the IS implantation procedure and device performance.	1-2 porcine per study	The implantation procedures in all animals were completed successfully and uneventful. The overall Genio® System showed favorable usability and

Study Type	Study Purpose	Study Sample Size	Results
			expected contraction of the genioglossus muscle and significant airway opening.
GLP Chronic Study – Migration and Stimulation Safety	- Evaluate the local effects of the IS on the target tissue (genioglossus muscle and hypoglossal nerve) under eight (8) weeks of periodic stimulation. - Evaluate the implant's location stability (i.e., migration) for a period of at least 12 weeks.	6 porcine	Long term stimulation was considered a non-irritant to the tissue and caused minimal local effects. The device is stable and did not migrate over time.
GLP Chronic Study – Migration	Perform a comparative evaluation of the IS Model #2954 during implantation for eight (8) weeks, demonstrating that the implant remains in place without migration, and the implant positions between the IS Model #2954 to the original IS (1st Generation) are equivalent.	6 porcine (4 IS Model #2954, 2 control)	There was no evidence of clinically relevant adverse pathological findings between control and test implanted animals. All implants were fully encapsulated, appeared stable, and were firmly secured to the surrounding tissues of the ventral tongue preventing any significant migration.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study ("DREAM") to establish a reasonable assurance of safety and effectiveness of bilateral Hypoglossal Nerve Stimulation with the Genio® System 2.1 to treat adult subjects with moderate to severe Obstructive Sleep Apnea (OSA) in the US, Belgium, Germany, and Australia under IDE G190068. Results from this clinical study were used to support the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between October 14, 2020, and March 3, 2024. The database for this PMA reflected primary endpoint data collected through Jan 6, 2025, and included 115 implanted patients. There were 22 investigational sites.

The DREAM study was a multi-center, prospective, open-label, non-randomized, single arm clinical study to demonstrate the safety and effectiveness of the Genio® dual-sided hypoglossal nerve stimulation system in treating moderate to severe OSA over a period of 12 months post-surgery.

Endpoints: The study had two co-primary efficacy endpoints: the first measured the percentage of responders at 12 months based on a 50% reduction in AHI4 (Apnea-Hypopnea Index based on 4% oxygen desaturation) and a remaining AHI4 of less than 20, and the second measured the percentage of responders based on a 25% reduction in ODI4 (Oxygen Desaturation Index based on 4% desaturation), both assessed with fixed therapeutic settings on full-night Polysomnography (PSG). The objective was to demonstrate at least 50% responders for both AHI4 and ODI4 at 12 months, with the study considered successful if the null hypotheses were rejected for both endpoints.

Sample Size: Sample size calculations used a one-sample exact binomial test with 80% statistical power and a one-sided 2.5% significance level. For the AHI4 endpoint, N=85 evaluable subjects were required to demonstrate superiority over the pre-specified performance goal of 50% responder rate, assuming a true responder rate of 65% under the alternative hypothesis. The ODI4 endpoint required a larger sample size of N=98 evaluable subjects, assuming a true responder rate of 64%. To account for approximately 15% non-evaluable subjects due to anticipated dropouts and missing data, a total of N=115 subjects were enrolled and implanted in the study (98/0.85).

Monitoring: An independent Data Safety Monitoring Board (DSMB) was established to review trial data, including safety events, protocol deviations, and device deficiencies, consisting of 4 members: 3 voting physicians (ENT/Sleep Medicine experts) and one non-voting biostatistician. A Clinical Events Committee (CEC) was also set up for this study to ensure objective and centralized review and adjudication of clinical adverse events occurring in this study. The CEC was composed of at least 3 members (3 physicians from the field of ENT and/or Sleep Medicine), who were independent from the study conduct. The CEC reviewed and adjudicated clinical adverse events.

Core Lab: All PSGs were scored by an independent Core Lab following AASM guidelines to minimize bias. Drug-Induced Sleep Endoscopy (DISE) was conducted on enrolled subjects with qualifying AHI scores to screen for complete concentric collapse (CCC).

Device Under Test: The study was conducted using the 1st Generation model of the IS ("original IS"). Although the original IS and IS Model #2954 differ in certain

characteristics, the two versions of the Genio® System implant were considered functionally equivalent in key areas such as: electronic circuitry, stimulation parameters used, active stimulation area of the electrodes, mode of communication with the AC Model #2364, and use of external components. The IS Model #2954 incorporated several design improvements including a hermetic ceramic enclosure (versus Parylene coated PEEK frame), a single-shoulder design for increased paddle flexibility (reduced from double-shoulder), slight increases in main body thickness and mass, and an extended service life from 3 years to at least 12 years. Based on all the non-clinical and pre-clinical testing conducted for IS Model #2954, it was concluded that the changes made for the IS Model #2954 did not impact the performance or functionality of the implant when compared to the original IS. Considering both the similarities between the original IS and the IS Model #2954 as well as the assessment of the design changes, the clinical data obtained with the original IS during the DREAM IDE study was considered leverageable for the IS Model #2954.

1. Inclusion and Exclusion Criteria

Enrollment in the DREAM study was limited to patients who met the following inclusion criteria:

- 22 to 75 years of age
- Body mass index of ≤ 32 kg/m2
- Cricomental space positive (≥ 0 cm)
- Have either not tolerated, have failed or refused positive airway pressure (PAP) treatments
- Moderate to severe OSA 15≤AHI4≤65 where combined central and mixed AHI < 25% of the total AHI
- Non-supine AHI > 10 events on the screening PSG or subject has either not tolerated, has failed or refused positional therapy
- Written informed consent for performing any study specific procedure
- Willing and capable of complying with all study requirements
- Willing to consent to long term follow-up of 5 years post-surgery

Patients were not permitted to enroll in the DREAM study if they met any of the following exclusion criteria:

- Inadequately treated sleep disorders other than OSA that would confound functional sleep assessment
- Night shift workers
- Taking medications that may alter consciousness, the pattern of respiration, or sleep architecture
- Major anatomical or functional abnormalities that would impair the ability of the Genio® System to treat OSA
- Significant comorbidities that contraindicate surgery or general anesthesia
- Prior surgery or treatments that could compromise the effectiveness of the Genio® System

- Have an Active Implantable Medical Device (AIMD) even if the device can be temporarily turned off
- Participation in another clinical study with an active treatment arm that could confound the results of the DREAM study
- Plan to become pregnant, currently pregnant, or breastfeeding during the study period
- The study did not include patients with complete concentric collapse at the soft palate level

2. Follow-up Schedule

The patients were scheduled for screening and baseline evaluations before implant and follow up post-surgery up to 12 months. Table 16 below lists the schedule of events up to and including the assessment of the primary and secondary endpoints at 6-months post-surgery.

Table 16. List of study procedures until the 6-month follow-up visit

Test / Evaluation	**Screening**	**Baseline**	**Implant**	**Week 1 Post-Op**	**Month 2 Follow Up**	**Month 3 Follow Up**	**Month 4 Follow Up**	**Month 5 Follow Up**	**Month 6 Follow Up**
Visit Window (Days)	**-90**	**-90**	**0**	**±5**	**±14**	**±14**	**±14**	**±14**	**±14**
Informed Consent Form (ICF) Signature	X								
Check Eligibility Criteria	X								
Demographic Data and Medical History	X								
Pregnancy Test	X[1]								
Surgical Consult and Mallampati Score	X								
Vital Signs	X	X	X[2]	X	X	X	X	X	X
Physical Examination	X								
Neck Circumference	X								
Functional Tongue Exam & Neurological Assessment	X		X[2]	X	X	X	X	X	X
EAT-10 questionnaire	X		X[2]	X	X	X	X	X	X
VHI-10 questionnaire	X		X[2]	X	X	X	X	X	X
Reflux Symptom Index questionnaire	X		X[2]	X	X	X	X	X	X
Height (screening only) & Weight	X		X						X
Cricomental Space	X								
Snoring Scoring, FOSQ-10, ESS and SNORE-25 Questionnaires	X								X
DISE	X[4,5]				X				O[3]

Test / Evaluation	Screening	Baseline	Implant	Week 1 Post-Op	Month 2 Follow Up	Month 3 Follow Up	Month 4 Follow Up	Month 5 Follow Up	Month 6 Follow Up
Home Sleep Test						O		O	
In-lab PSG	X	X					X		X
Implantation Procedure			X						
Subject Card			X[7]						
Pain Visual Analog Scale (VAS)			X[7]	X	X				
Device Activation and Subject Training					X[6]				
Awake Titration					X	X	X	X	X
Asleep Titration							X		X
Usability Questionnaire							X		X
Subject Satisfaction Questionnaire									X
Dispense / Collect Subject Diary[8]					X	X	X	X	X
Device Check					X	X	X	X	X
Adverse Events	X	X	X[7]	X	X	X	X	X	X
Device Deficiencies	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X[7]	X	X	X	X	X	X

X = required
O = optional

[1] If applicable (only for women of childbearing potential). A urine pregnancy test is sufficient to determine participation. A serum pregnancy test instead of a urine pregnancy test should only be considered if required by country, local or ethic committee regulations. Female subjects are strongly advised to use effective contraception during the course of the research.

[2] EAT-10, Reflux Symptom Index, VHI-10, Vital signs and functional tongue exam & neurological assessments will be completed both prior to surgery and prior to discharge.

[3] In case DISE is performed prior to the PSG (where applicable), DISE shall be conducted at least 12 hours prior to the PSG.

[4] Screening DISE can only be performed if the Core lab confirmed subject has successfully passed the screening PSG.

[5] A previously performed DISE can be used as the Screening DISE, if it has been performed within 6 months prior to enrollment, the video is available and can be scored by the Core Lab, and if from the date of the DISE to enrollment date:

a. there has been no change in subject BMI >1kg/m^2,
b. the subject has not undergone upper airway surgery, including nasal surgery, and
c. there has been no significant change in medical history or other reason that would impact the results of the DISE, as determined by the Investigator.

[6] Subject may be retrained if needed.

[7] Assessments to be performed after surgery and prior to discharge.

[8] Subjects will complete the diary daily.

Note: Routine tests could be done before anesthesia and surgery, per each hospital's standard of care.

At the 6-month visit, the investigator assessed if the therapy was optimized based on a positive change in AHI and ODI from baseline. If therapy was considered optimized, study visits were

scheduled at 9- and 12-months. If the therapy was not optimized, study visits were scheduled at 8-, 10- and 12-months. The procedures that were performed after the 6-month visit are presented in Table 17 below.

Table 17. List of study procedures after the 6-month follow-up visit

Test / Evaluation	If therapy not optimized @ 6-month		If therapy optimized @ 6-month	Month 12 Follow Up
	Month 8 Follow Up	Month 10 Follow Up	Month 9 Follow Up	
Visit Window (Days)	**±14**	**±14**	**±14**	**±30**
Vital Signs	X	X	X	X
Functional Tongue Exam & Neurological Assessment	X	X	X	X
EAT-10 questionnaire	X	X	X	X
VHI-10 questionnaire	X	X	X	X
Reflux Symptom Index questionnaire	X	X	X	X
Weight				X
Snoring Scoring, FOSQ-10, ESS and SNORE-25 Questionnaires	X	X	X	X
In-lab PSG	X	X	X	X
Asleep Titration	X	X	X	
DISE	O[1]		O[1]	
Awake Titration	X	X	X	X
Usability Questionnaire	X	X	X	X
Satisfaction Questionnaire				X
Dispense / Collect Subject Diary[2]	X	X	X	X
Device Check	X	X	X	X
Adverse Events	X	X	X	X
Device Deficiencies	X	X	X	X
Concomitant Medications	X	X	X	X
Study Exit	X[3]	X[3]	X[3]	X[3]

X = required
O = optional
[1] In case DISE is performed prior to the PSG (where applicable), DISE shall be conducted at least 12 hours prior to the PSG.
[2] Subjects will complete the diary daily.
[3] If applicable.

3. Clinical Endpoints

Safety Endpoints

With regards to safety, evaluation was conducted using the incidence of device and/or procedure serious events recorded during the study for a period of 12 months post-surgery. All adverse events were adjudicated by an independent Clinical Events Committee (CEC). An independent Data & Safety Monitoring Board (DSMB) reviewed the accumulated safety data and assessed the validity and integrity of the clinical study data.

Co-Primary Effectiveness Endpoints

- AHI4: percentage of responders at 12 months based on AHI4, a responder being defined as a participant who satisfies the following criteria: at least a 50% reduction from the average AHI4 of screening and baseline to 12 months post-surgery and a residual AHI4 less than 20 at the 12-month visit (i.e., "Sher Criteria"), as measured with fixed therapeutic settings using full-night PSG (all scored by an independent core laboratory)

- ODI4: percentage of responders at 12 months based on ODI4, a responder being defined as a participant who satisfies the following criterion: at least a 25% reduction from the average ODI4 of screening and baseline to 12 months post-surgery, as measured with fixed therapeutic settings using full-night PSG (all scored by an independent core laboratory).

Secondary Effectiveness Endpoints

Six secondary effectiveness endpoints were identified in the DREAM study protocol:

1. Mean change in the OSA-specific quality of life measured by the SNORE-25 instrument at the 12-month visit compared to screening.
2. Mean change in the hypoxemic burden measured by the percentage of sleep time with oxyhemoglobin saturation < 90% at the 12-month PSG compared to the average of screening and baseline.
3. Mean change in the intermittent hypoxia measured by the ODI4 at the 12-month PSG compared to the average of screening and baseline.
4. Mean change in the sleep-specific function measured by the Functional Outcomes of Sleep Questionnaire (FOSQ-10) at the 12-month visit compared to screening.
5. Mean change in the sleep propensity measured by the ESS at the 12-month visit compared to screening.
6. Mean change in OSA severity measured by the AHI4 at the 12-month PSG compared to the average of screening and baseline.

Success/failure criteria

Patient success was defined as clinically significant reduction in OSA and improvements in overall sleep quality.

The study objective was to demonstrate at least 50% responder rates at 12 months (pre-specified performance goal) for both co-primary endpoints: AHI4-based responders (first co-primary endpoint) and ODI4-based responders (second co-primary endpoint). Study success required rejection of the null hypotheses for both co-primary endpoints as defined below.

The statistical hypotheses for the first co-primary endpoint were the following:

- H01 (null hypothesis): Percentage of responders at Month 12 based on AHI4 ("Sher Criteria") < 50%
- H11 (alternative hypothesis): Percentage of responders at Month 12 based on AHI4 ("Sher Criteria") ≥ 50%

The statistical hypotheses for the second co-primary endpoint were the following:

- H02 (null hypothesis): Percentage of responders at Month 12 based on ODI4 < 50%
- H12 (alternative hypothesis): Percentage of responders at Month 12 based on ODI4 ≥ 50%

To claim success in meeting secondary effectiveness endpoints, all six secondary endpoints described above were required to be met to preserve the overall Type I error rate of 2.5%.

B. Accountability of PMA Cohort

A total of 687 subjects were enrolled according to protocol-defined procedures. A total of 568 subjects (82.7%) were screen failures and did not receive an implant. A total of 115 subjects (16.7%) from 19 investigative sites had an attempted implant with 113 (16.4%) of those successfully implanted with the Genio® System. Figure 14 includes accountability of the subject disposition and analysis cohorts.

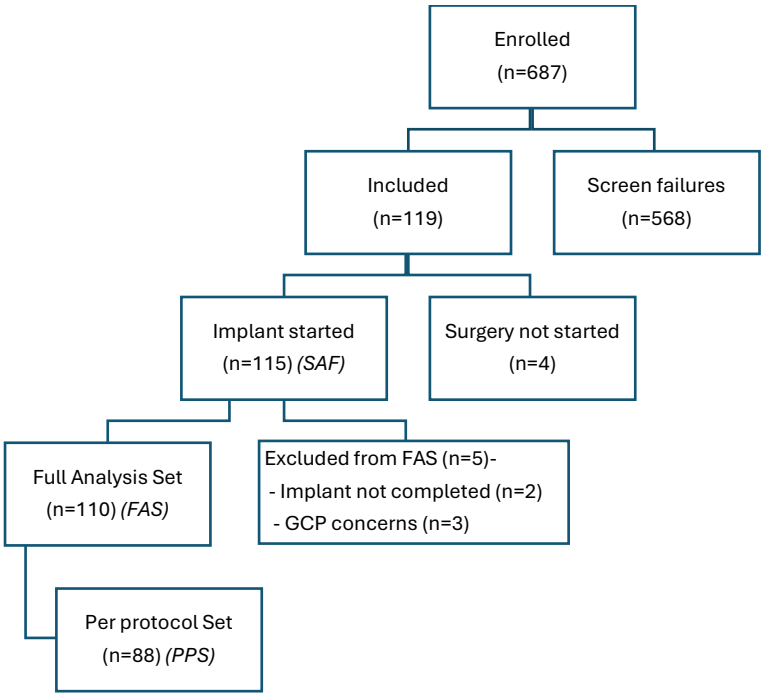

Figure 14: Subject disposition, analysis cohorts.

The following sets of population were used in the analysis of the study: the Enrolled set, the Safety (SAF) set, the Full Analysis (FA) set, and the Per Protocol (PP) set.

Enrolled Set (N=687)
The Enrolled set included all subjects with informed consent form signed. This set was used for the listings of adverse events as some adverse events may have started before the implant procedure.

Safety Set (SAF) (N=115)
The SAF set included all subjects who underwent the implant procedure (implant surgery started, whether the device was implanted or not). This set was used for description of demographic and baseline characteristics as well as for analyses of safety assessments.

Full Analysis Set (FAS) (N=110)
The FA included all subjects who successfully completed the implant procedure. Additionally, the three subjects successfully implanted in Australia were not included in FA set due to the unmonitored status of their data (Good Clinical Practice (GCP) deviation). They were subsequently excluded from the effectiveness analyses.

Per Protocol Set (PP) (N=88)
The per-protocol set (PP) included all subjects from the FA set who performed the 12-month PSG with available values for primary endpoints (AHI4 and ODI4) and without any critical major protocol deviations. In case the PP set differs from the FA set, the PP set may be used for description of demographic and baseline characteristics as well as for analyses of effectiveness assessments.

Statistical Analysis of Analysis Sets
The SAF will be used for the analysis of safety assessments. Effectiveness assessments will be analyzed on the FA (primary analysis), on the PP (sensitivity analysis), and on the SAF (sensitivity analysis for co-primary endpoints).

At the time of database lock, of the 115 patients enrolled in the PMA study, 93 patients were available for analysis at the completion of the study, the 12-month post-operative visit. Of the 115 subjects who underwent attempted implantation, 93 completed the M12 clinic visit and 89 also completed an M12 PSG. The remaining 27 patients did not undergo a final PSG due to: GCP-related withdrawals (3), aborted surgery (2), major protocol deviation (1), lost to follow-up (4), consent withdrawal (6), and missed M12 visits due to adverse events, device deficiencies, or visits occurring outside the protocol window (10). Table 18 summarizes the cumulative implanted subject accountability by visit.

Table 18. Cumulative Implanted Subjects Accountability by Visit – SAF (N=115)

Subjects	Implant	1-wk	M2	M3	M4	M5	M6	M8*	M9	M10*	M12
Visit at interval	115 (100%)	114 (99.1%)	112 (97.4%)	109 (94.8%)	107 (93.0%)	98 (85.2%)	104 (90.4%)	52 (45.2%)	45 (39.1%)	51 (44.3%)	93 (80.9%)
Visit in window	55	107	105	100	92	87	78	33	38	38	77
Visit outside window	60	7	7	9	15	11	26	19	7	13	16
Missed Visit	0	1	0	2	2	9	1	4	1	5	2

* M8 and M10 visits conducted if therapy not optimized at Month 6 visit.

C. Study Population Demographics and Baseline Parameters

The demographics of the 115 subjects implanted with the Genio® system are presented in Table 19.

Table 19. DREAM subject demographics

Demographic Outcomes	Mean ± SD (N = 115)	Median (Min; Max)
Age, year	56.8 ± 7.3	57 (36;71)
Male, gender	70.4% (81/115)	NA
Body Mass Index, kg/m^2	28.50 ± 2.63	28.7 (21.7; 32.0)
BP Systolic, mmHg	132.6 ± 16.5	131
BP Diastolic, mmHg	79.9 ± 10.0	80

Neck Circumference, cm	40.55 ± 5.73	40.6 (30.5; 86.4)
Race: Caucasian	93.9% (108/115)	NA
Race: Asian	0.9% (1/115)	NA
Race: Black or African American	3.5% (4/115)	NA
Race: Other	1.7% (2/115)	NA

Even though most patients in the study were male and Caucasian, it is expected that the Genio® System would be effective in other populations as the mechanism of action involving bilateral hypoglossal nerve stimulation to activate tongue muscles is consistent across demographic groups.

Table 20. Baseline AHI ranges (FAS N=110)

Baseline AHI ranges	n (%)
$X \leq 5$	0 (%)
$5 < X < 15$ (mild OSA)	10 (9.1%)
$15 \leq X < 30$ (moderate OSA)	60 (54.5%)
$X \geq 30$ (severe OSA)	40 (36.4%)

The study included 10 subjects with a baseline AHI of less than 15 events/hr. This outcome was a result of the following aspects of the study design -

- All subjects had to meet the inclusion criteria of at least moderate OSA in their Screening PSG; no such requirement was placed on the pre-operative PSG
- Night-to-night variability of AHI can skew or misrepresent the burden of OSA even if AHI4 and supine sleep times are similar across multiple nights
- Results from the two PSGs were averaged to obtain a baseline AHI

Although this computation was not used in the study, when their historical PSGs were also included in computing the average AHI, most of these subjects presented with moderate OSA. Therefore, the inclusion of these subjects in the study was justified.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on an assessment of all reported adverse events.

Adverse events that occurred in the PMA clinical study

Safety parameters were evaluated based on the incidence of device or procedure-related adverse events recorded during the 12-month post-surgical period. A total of 394 adverse events occurred during the 12-month post-implantation period, including 252 non-serious adverse events in 85 subjects (73.9%) and 13 serious adverse events in 13 subjects (11.3%)* related to device or procedure. All adverse events observed in the study are summarized in Table 21 below.

Table 21: Overview of Adverse Events through M12 visit – Safety Set (N=115)

Adverse events	Non-device-related Non-procedure-related m (n, %)	Device or Procedure-related m (n, %)
Non-serious	126 (59, 51.3%) (AE)	252 (85, 73.9%) (AE)
Serious	3 (2, 1.7%) (SAE)	13 (13, 11.3%)* (SAE)

n: number of subjects with at least one event
% = (n row / N column x 100)
m: number of events
Note: A same subject can have more than one event
* The 13 serious adverse events include 1 case of repositioning surgery (procedure-related) and 4 cases of replacement surgery (device-related) that were neither classified by the Study Investigator nor adjudicated by the Clinical Events Committee (CEC) as serious adverse events. If these events are excluded from the list of SAEs, the overall incidence of device- and/or procedure-related SAEs up 12-months would be 7% (device-related: 1.7%, device- and procedure-related: 0.9%, procedure-related: 4.3%). See Table 24 for description of SAEs.

All serious and non-serious adverse events observed in the clinical study through the 12-month follow-up in the safety set of 115 patients are listed below.

Table 22. Occurrence rate of Non-Serious and Serious Adverse Events through M12 visit – Safety Set (N=115)

Non-Serious Adverse Events	Subjects with Events (%)
Application site irritation	28 (24.3%)
Dysphagia	21 (18.3%)
Incision site swelling	19 (16.5%)
Medical device discomfort	17 (14.8%)
Glossodynia	15 (13.0%)
Implant site hypoaesthesia	7 (6.1%)
Procedural pain	7 (6.1%)
Dysphonia	6 (5.2%)
Oropharyngeal pain	6 (5.2%)
Post procedural contusion	6 (5.2%)
Tongue movement disturbance	5 (4.3%)
Tongue exfoliation	4 (3.5%)
Medical device pain	4 (3.5%)
Application site reaction	4 (3.5%)
Glossitis	4 (3.5%)

Non-Serious Adverse Events	Subjects with Events (%)
Cough	3 (2.6%)
Odynophagia	3 (2.6%)
Pain in jaw	3 (2.6%)
Post procedural swelling	3 (2.6%)
Speech disorder	3 (2.6%)
Dry mouth	2 (1.7%)
Dysarthria	2 (1.7%)
Ear discomfort	2 (1.7%)
Epistaxis	2 (1.7%)
Headache	2 (1.7%)
Hypoaesthesia oral	2 (1.7%)
Implant site irritation	2 (1.7%)
Incision site pain	2 (1.7%)
Neck pain	2 (1.7%)
Post procedural fever	2 (1.7%)
Procedural headache	2 (1.7%)
Procedural site reaction	2 (1.7%)
Sleep disorder	2 (1.7%)
Somnolence	2 (1.7%)
Tinnitus	2 (1.7%)
Tongue spasm	2 (1.7%)
Ageusia	1 (0.9%)
Anxiety	1 (0.9%)
Application site infection	1 (0.9%)
Application site rash	1 (0.9%)
Application site ulcer	1 (0.9%)
Atrial fibrillation	1 (0.9%)
Back pain	1 (0.9%)
Dermatitis contact	1 (0.9%)
Dizziness	1 (0.9%)
Dyspepsia	1 (0.9%)
Ear pain	1 (0.9%)
Fatigue	1 (0.9%)
Foreign body	1 (0.9%)
Gastroesophageal reflux disease	1 (0.9%)
Hemorrhage	1 (0.9%)
Hypoaesthesia	1 (0.9%)
Implant site infection	1 (0.9%)
Incision site hematoma	1 (0.9%)
Ingrown hair	1 (0.9%)

Non-Serious Adverse Events	Subjects with Events (%)
Jaw clicking	1 (0.9%)
Jaw disorder	1 (0.9%)
Muscle contractions involuntary	1 (0.9%)
Musculoskeletal discomfort	1 (0.9%)
Panic attack	1 (0.9%)
Paranesthesia	1 (0.9%)
Phlebitis	1 (0.9%)
Plicated tongue	1 (0.9%)
Post procedural diarrhea	1 (0.9%)
Post procedural discomfort	1 (0.9%)
Presyncope	1 (0.9%)
Procedural nausea	1 (0.9%)
Sensation of foreign body	1 (0.9%)
Swelling	1 (0.9%)
Swollen tongue	1 (0.9%)
Tongue discomfort	1 (0.9%)
Tooth disorder	1 (0.9%)
Serious Adverse Events	**Subjects with Events (%)**
Device dislocation	2 (1.7%)
Dysphagia	2 (1.7%)
Bundle branch block left	1 (0.9%)
Device extrusion	1 (0.9%)
Epistaxis	1 (0.9%)
Incision site hematoma	1 (0.9%)
Repositioning surgery*	1 (0.9%)
Replacement surgery*	4 (3.5%)

* The 1 case of repositioning surgery and 4 cases of replacement surgery were neither classified by the Study Investigators nor adjudicated by the Clinical Events Committee (CEC) as serious adverse events.

Serious Adverse Events

There were 16 serious adverse events, of which 3 events (2.6%) were unrelated to the device/procedure, while 13 events (11.3%) were device and/or procedure-related. The device/procedure-related SAEs comprised 6 device-related events (5.2%), 6 procedure-related events (5.2%), and 1 event related to both device and procedure (0.9%). Additionally, 5 surgical interventions were performed (1 repositioning, 4 replacement surgeries), with 2 successful replacements and 2 unsuccessful due to scar tissue. Table 23 provides the summary of all SAEs through 12 months post-implantation.

Table 23: SAE Summary through 12 Months Post Implant – SAF Set (N=115)

Serious Events	m (n,%)
Unrelated to Genio® Device and Unrelated to Implant Procedure – Serious Adverse Events (SAE)	3 (2, 1.7%)
Genio® Device-Related and/or Implant Procedure-Related – Serious Adverse Events (SAE)	13 (13, 11.3%)*
• Genio® Device-Related	6 (6, 5.2%)*
• Genio® Implant Procedure-Related	6 (6, 5.2%)*
• Genio® Device and Implant Procedure-Related	1 (1, 0.9%)*

n: number of subjects with at least one event
% = (n row / N column x 100)
m: number of events
Note: A same subject can have more than one event
* The 13 serious adverse events include 1 case of repositioning surgery (procedure-related) and 4 cases of replacement surgery (device-related) that were neither classified by the Study Investigators nor by the Clinical Events Committee (CEC) as serious adverse events. If these events are excluded from the list of SAEs, the overall incidence of device- and/or procedure-related SAEs up 12-months would be 7% (device-related: 1.7%, device- and procedure-related: 0.9%, procedure-related: 4.3%).

Table 24 provides a detailed description of all device and/or procedure-related SAEs through 12 months post-implant. Among the 10 surgical interventions, one subject experienced an unanticipated serious adverse device effect where the implantable stimulator protruded through the back of the gum. An unrelated dental procedure may have caused device displacement from its original location, resulting in protrusion through the floor of the mouth and subsequent explantation. In two cases, device migration occurred prior to activation, resulting in lack of stimulation and subsequent explantation. One patient underwent device repositioning and four patients underwent device replacement procedures. Two replacements were successful, while two were unsuccessful due to existing scar tissue that prevented replacement, leading to device explantation.

Table 24. Device and/or Procedure-related Serious Adverse Events 12 Months Post Implant

Description of SAE	Detailed Event Description
Incision Site Hematoma	Two days post-implant surgery, patient had developed hematoma at the surgical incision site with increased neck swelling and worsening bruising of the neck requiring surgical evacuation of the hematoma. The event was resolved without sequelae 4 days later. Patient continued in the study through the 18-month visit.

Description of SAE	Detailed Event Description
Dysphagia	Patient reported inability to swallow while in the recovery room post-implant and was discharged 11 days later in stable condition. The patient exited the study 10 days after discharge with the event ongoing and opted to keep the device implanted.
Dysphagia	Patient experienced impaired swallowing on the day of implant surgery. Hospital stay was extended due to trouble related to speech and swallowing from poor tongue motion. Edema was noted at the floor of the mouth edema. The event was fully resolved without sequelae a month later and assessed. Patient remains active in the study through the M36 visit.
Epistaxis	Patient experienced epistaxis on the right side 5 days post-implant surgery and was admitted to the emergency room with intermittent nasal bleeding from abrasions secondary to attempted nasal intubation during the implant surgery. The patient was discharged 2 days later; however, intermittent nasal bleeding persisted for approximately 50 days after discharge. Event was fully resolved without sequelae. The patient remained in the study until the M24 visit and was exited 4 months after with the device kept implanted.
Bundle Branch Block Left	Patient developed ventricular ectopy and new left bundle branch block at the end of the implant surgery procedure. The patient was admitted for cardiac monitoring and discharged the next day with the event fully resolved without sequalae. Patient remained active in the study through the M18 visit and was exited from the study 2 months later due to lost to follow-up with the device kept implanted.
Device Dislocation (Explant Surgery at 8 months)	Patient experienced a lack of stimulation approximately 253 days post implant surgery. A revision surgery was performed and the Implantable Stimulator (IS) was found to have migrated to one side. Due to the tight space between the hyoid bone and mandible, replacement or revision was not possible and the device was explanted without further complications. Patient exited the study a few months later.
Device Extrusion (Explant Surgery at 10 months)	Patient reported the Implantable Stimulator (IS) was protruding through the back of the gum approximately 310 days post implant surgery. Two months prior to this event, patient underwent a planned dental implant procedure to the floor of the mouth which was followed by a significant change in the stimulation amplitude. The IS was surgically removed about 2 weeks later without complications. Patient exited the study 3 weeks post explant surgery.

Description of SAE	Detailed Event Description
Device Dislocation (Explant Surgery at 2 months)	Patient reported increased swelling under the chin without pain, approximately 2 months post-implant surgery and reported no sensation or physical response to stimulation. X-ray showed disoriented and migrated device. Patient underwent explant surgery a month later without complications. Patient exited the study 2 weeks post-surgery.
Replacement Surgery at 6 Months *	Patient experienced inconsistent stimulation with suspected retrusor branch of the HGN included during implant as the Investigator did not observe straight tongue protrusion. During surgical intervention no migration was identified but excessive scarring was noted, preventing replacement. Device was explanted without complications.
Replacement Surgery at 6 Months *	Patient reported stimulation discomfort and intermittent stimulation. External component troubleshooting revealed atypical device activity. During surgical intervention it was confirmed the device had not migrated. The device was successfully replaced without complication with consistent stimulation observed from new device during intra-operative testing. Patient continued in the study.
Replacement Surgery at 11 Months *	Patient experienced inconsistent stimulation that could not be resolved with external component troubleshooting. During surgical intervention the device was tested with no response. Device was successfully removed and replaced with consistent stimulation observed from new device during intra-operative testing. Patient continued in the study.
Replacement Surgery at 12 Months *	Patient experienced loss of stimulation that could not be resolved with external component troubleshooting. Migration noted in X-ray with migration of right paddle confirmed during intervention. Excessive scarring prevented replacement and device was explanted without complications.
Repositioning Surgery at 9 Months *	Patient had mixed hypoglossal nerve activation on the left noted when the device was activated. The Investigator repositioned the device to exclude retrusor branches from receiving stimulation.

* The 1 case of repositioning surgery and 4 cases of replacement surgery were neither classified by the Study Investigators nor adjudicated by the Clinical Events Committee (CEC) as serious adverse events.

Table 25 provides the Genio® device or implant related procedure serious adverse events by time of event onset.

Table 25: Serious Adverse Events by Period – Safety Set (N=115)

Event	m (n,%)
At least one SADE	13 (13, 11.3%)*
Pre-implant	0 (0, 0.0%)
0-30 days post implant	5 (5, 4.3%)
30 days to 12 months post implant	8 (3, 6.9%)*

n: number of subjects with at least one event
% = (n row / N column x 100)
m: number of events
Note: A same subject can have more than one event
* Includes 1 case of repositioning surgery (procedure related) and 4 cases of replacement surgery (device-related) that were neither classified by the Study Investigators nor adjudicated by the Clinical Events Committee (CEC) as serious adverse events.

Non-Serious Adverse Events

Out of the 115 implanted subjects, 85 (73.9%) experienced a total of 252 non-serious device and/or implant procedure-related AEs. Table 26 provides the summary of all non-serious AEs through 12 months post-implantation.

Table 26: Non-Serious AE Summary through 12 Months Post Implant (CEC)– SAF (N=115)

Adverse Events	m (n,%)
Unrelated to Genio® Device and Unrelated to Implant Procedure – Adverse Events (AE)	126 (59, 51.3%)
Genio® Device-Related and/or Implant Procedure-Related – Adverse Device Effect (ADE)	252 (85, 73.9%)
• Genio® Device-Related	134 (66, 57.4%)
• Genio® Implant Procedure-Related	107 (46, 40.0%)
• Genio® Device and Implant Procedure-Related	11 (9, 7.8%)

n: number of subjects with at least one event
% = (n row / N column x 100)
m: number of events
Note: A same subject can have more than one event

Table 27 presents the non-serious procedure-related events sorted by time frame.

Table 27: Non-Serious Implant Procedure-Related Adverse Events by Timepoint – SAF (N=115)

Timepoint for AE	m (N,%)
0-30 days post implant	100 (44, 38.3%)
> 30 days post implant	7 (7, 6.1%)

n: number of subjects with at least one event
% = (n row / N column x 100)
m: number of events
Note: A same subject can have more than one event

As expected, majority of non-serious implant procedure-related events (100 of 107 or 93.5%) occurred within 30 days post-implant.

Since the Genio® system was activated about 8 weeks after the implant surgery, it was expected that the majority of non-serious device-related AEs would occur after this timeframe. Table 28 below shows that 134 of 134 (100%) events occurred more than 30 days post-surgery. There were no non-serious device-related AEs reported within 30 days post-implant.

Table 28: Non-Serious Device-Related Adverse Events by Timepoint – SAF (N=115)

Timepoint for AE	m (N, %)
0-30 days post implant	0 (0, 0.0%)
> 30 days post implant	134 (66, 57.4%)

n: number of subjects with at least one event
% = (n row / N column x 100)
m: number of events
Note: A same subject can have more than one event

There were 11 non-serious device and implant procedure related AEs, the majority of which occurred more than 30 days post-implant.

Table 29: Non-Serious Device and Implant-Procedure Related Events by Timepoint – SAF (N=115)

Timepoint for AE	m (N, %)
0-30 days post implant	2 (2, 1.7%)
> 30 days post implant	9 (8, 7.0%)

n: number of subjects with at least one event
% = (n row / N column x 100)
m: number of events

Among the device-related non-serious events, 24.3% of patients experienced local skin irritation due to the Disposable Patch, which resolved in all cases. The 4 most frequent non-serious device and/or procedure-related AEs through the subjects' 12-month follow-up are presented in Table 30.

Table 30: Most frequent Non-Serious Device and/or Procedure Related Events – Safety Set (N=115)

Description of AE	m (n, %)
Application site irritation	37 (28, 24.3%)
Dysphagia	21 (20, 17.4%)
Incision site swelling	19 (18, 15.7%)
Medical device discomfort	19 (17, 14.8%)

n: number of subjects with at least one event
% = (n row / N column x 100)
m: number of events
Note: A same subject can have more than one event

Post-Month 12 Safety Data

A subset of active study subjects completed 24-month and 36-month timepoints as part of the DREAM study's long-term follow-up of up to 5 years, as shown in Table 31 below.

Table 25. Summary of Study Subjects with Post M12 Study Timepoints

Months	Subjects
24-Month	74
36-Month	30
48-Month	0

A summary of safety events post-Month 12 has been provided in the Table 32 below. Post-Month 12, device or procedure-related adverse events included 29 non-serious events in 22 subjects (19.1%) and 5 serious adverse events in 5 subjects (4.3%). The serious adverse events comprised 2 replacement surgeries and 3 explant surgeries.

Table 26. Adverse Event Summary Post-Month 12

Adverse events	Non-device-related Non-procedure-related m (n, %)	Device or Procedure-related m (n, %)
Non-serious	97 (46, 40.0%) (AE)	29 (22, 19.1%) (AE)
Serious	11 (5, 4.3%) (SAE)	5 (5, 4.3%)* (SAE)

n: number of subjects with at least one event
% = (n row / N column x 100)
m: number of events
Note: A same subject can have more than one event
* The 5 serious adverse events include 2 cases of replacement surgery and 3 cases of explant surgery that were neither classified by Study Investigators nor adjudicated by the Clinical Events Committee (CEC) as serious adverse events

Table 33 below presents a summary of all serious adverse events related to surgical interventions experienced by subjects in the DREAM study Post-Month 12 .

Table 33. Serious Adverse Events Related to Surgical Interventions Post-Month 12 *

Post-Surgical Intervention	Reason for Surgical Intervention	Surgical Intervention / Complications	Surgical Outcome	Subject Disposition
Explant Surgery at 17 Months	Device Deficiency: Subject feeling inconsistent stimulation. Unable to resolve with external component troubleshooting. Investigator and patient decided to explant device.	During the intervention, it was confirmed that the device had not migrated. Device tested and no stimulation observed. Device explanted without complication.	The device was successfully explanted.	No adverse events observed or reported post-operatively.
Explant Surgery at 22 Months	Device Deficiency: No stimulation felt. Unable to be resolved through external component troubleshooting. Decision was made to explant.	The device was explanted without complication.	The device was successfully explanted.	No adverse events observed or reported post-operatively.

Post-Surgical Intervention	Reason for Surgical Intervention	Surgical Intervention / Complications	Surgical Outcome	Subject Disposition
Explant Surgery at 28 Months	Device Deficiency: Inconsistent connectivity of device. External component troubleshooting did not resolve the issue which led to deeming it to be IS related. The subject elected to have the device explanted.	During the intervention, calcification was noted on the body of the device. The device was removed without complication.	The device was successfully explanted.	No adverse events observed or reported post-operatively.
Replacement Surgery at 16 Months	Device Deficiency: Potential migration of the device after MVA. Following the incident, subject experienced inconsistent stimulation. Unable to resolve with external component troubleshooting.	Migration confirmed during intervention. Scaring and encapsulation were present, device replaced successfully with no complications.	Consistent stimulation observed from new device during intra operative testing.	Subject continued in the study. No adverse events observed or reported post-operatively.
Replacement Surgery at 21 Months	Device Deficiency: Subject feeling inconsistent stimulation. Unable to resolve with external component troubleshooting.	The device was successfully replaced without complications.	Consistent stimulation observed from new device during intra – operative testing.	No adverse events observed or reported post-operatively.

* The 5 serious adverse events include 2 cases of replacement surgery and 3 cases of explant surgery that were neither classified by the Study Investigators nor adjudicated by the Clinical Events Committee (CEC) as serious adverse events.

2. Effectiveness Results

The analysis of effectiveness was based on the full analysis set (FAS) of 110 with worst-case imputation, and per protocol set (PPS) of 88 evaluable patients at the 12-month time point. Additional sensitivity analysis was performed in the safety analysis set (SAF) of 115 subjects. Key effectiveness outcomes are presented in Tables 34 to 36.

Primary Effectiveness Outcomes

The primary effectiveness objective of the DREAM trial was to evaluate if the Genio® system

provided a clinically significant reduction in OSA in adult subjects. This evaluation was performed by comparing the AHI and ODI at baseline and at the 12-month follow-up visit. The observed co-primary endpoints, AHI4 and ODI4 responder rates for the various analysis sets, is shown in Table 34, Table 35 and Table 36 respectively:

Table 34: Co-Primary Endpoints: AHI4 and ODI4 Responder Rate Analyses (Worst-Case Imputation) – FAS (N=110)

Primary Endpoint	Responder Rate	Performance Goal	Lower 2-sided 95% Confidence Level	*p* value
AHI Response Rate M12	66.4% (73/110)	50%	56.7%	< 0.001
ODI Response Rate M12	74.5% (82/110)	50%	65.4%	< 0.001

Table 35: Co-Primary Endpoints: AHI4 and ODI4 Responder Rate Analyses – PP Set (N=88)

Primary Endpoint	Responder Rate	Performance Goal	Lower 2-sided 95% Confidence Level	*p* value
AHI Response Rate M12	81.8% (72/88)	50%	72.2%	0.001
ODI Response Rate M12	92.0% (81/88)	50%	84.3%	< 0.001

Table 36: Co-Primary Endpoints: AHI4 and ODI4 Responder Rate Analyses (Worst-Case Imputation) – SAF (N=115)

Primary Endpoint	Responder Rate	Performance Goal	Lower 2-sided 95% Confidence Level	*p* value
AHI Response Rate M12	63.5% (73/115)	50%	54.0%	0.002
ODI Response Rate M12	71.3% (82/115)	50%	62.1%	< 0.001

The same results described in the tables above are also displayed in Figure 15 (AHI) and Figure 16 (ODI) below.

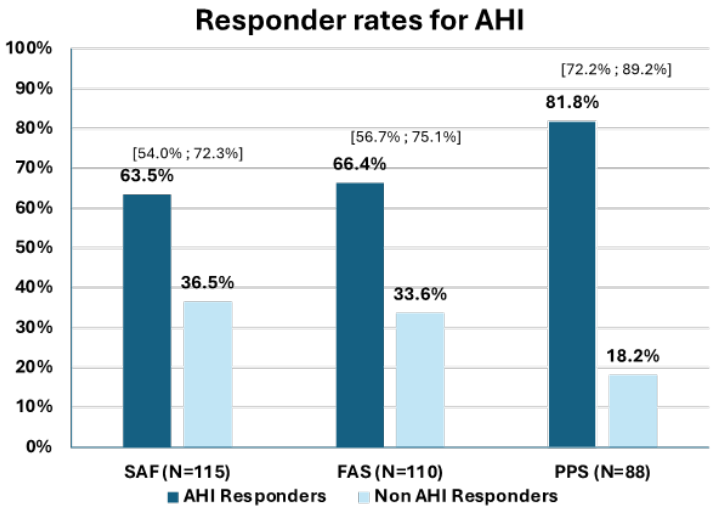

Figure 15. Co-Primary Endpoints Results: AHI

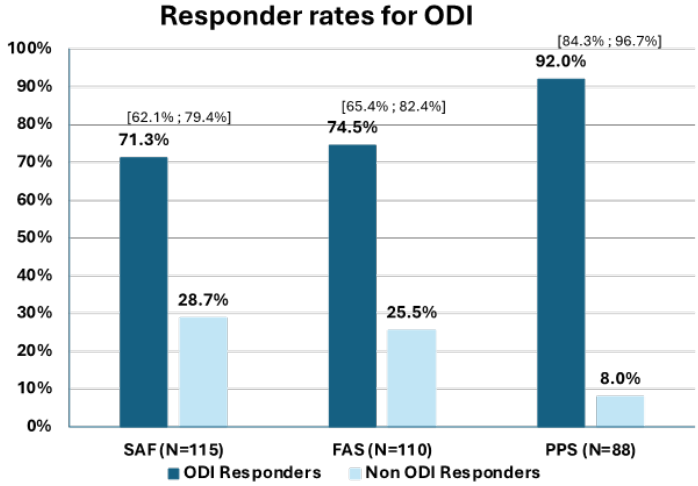

Figure 16. Co-Primary Endpoints Results: ODI

The DREAM pivotal trial met both co-primary effectiveness endpoints.
Both primary endpoints were tested at a 2.5% level of significance and both effectiveness objectives were met, thereby preserving an overall significance level of 2.5%.

Secondary Effectiveness Outcomes

Six secondary effectiveness endpoints were identified in the DREAM study protocol. In order to claim success in meeting a secondary effectiveness endpoint, all preceding secondary endpoints needed to be met in order to preserve an overall Type I error rate of 2.5% (hierarchical testing). Analyses were performed on subjects with values at the baseline and Month 12 visits.

The DREAM Study pivotal trial met all six secondary effectiveness endpoints. A summary of the secondary endpoint results, including their clinical significance, is presented below in Table 37.

Table 37. Summary of Secondary Endpoint Results

Endpoint	Clinical Significance	Baseline N / Mean ± standard deviation	Month 12 N / Mean ± standard deviation	Change from baseline to Month 12 N / Mean ± standard deviation / p-value / *CI*
SNORE-25 total score	Encompasses quality of sleep and life for both the patient and their bad partner	FAS: 110 / 1.61 ± 0.88 PPS: 88 / 1.62 ± 0.90	FAS: 89 / 0.59 ± 0.62 PPS: 86 / 0.60 ± 0.63	FAS: 89 / -1.02 ± 0.84 / < 0.001 / -1.20 ; -0.85 PPS: 86 / -1.03 ± 0.85 / < 0.001 / -1.21 ; -0.85
Total sleep time SaO2 < 90% (%)	Measure of hypoxic burden and is correlated with cardiovascular mortality in OSA	FAS: 110 / 12.44 ± 12.75 PPS: 88 / 11.98 ± *12.34*	FAS: 89 / 5.02 ± 8.44 PPS: 88 / *5.04 ± 8.49*	FAS: 89 / -6.90 ± 10.65 / <0.001 / -9.14 ; -4.66 PPS: 88 / -6.94 ± 10.71 / <0.001 / -9.20 ; -4.67
Mean reduction in Oxygen Desaturation Index (ODI) (events/hour)	Indicator of reduction in cardiovascular risk and improvement in quality of life	FAS: 110 / 26.95 ± 13.78 PPS: 88 / 26.83 ± 14.43	FAS: 89 / 9.15 ± 9.60 PPS: 88 / 9.16 ± 9.66	FAS: 89 / -17.71 ± 14.62 / <0.001 / -20.79 ; -14.63 PPS: 88 / -17.67 ± 14.70 / <0.001 / -20.78 ; -14.56
FOSQ-10 total score	Quantifies the effects of fatigue on daily activities	FAS: 109 / 15.92 ± 2.94 PPS: 87 / 16.06 ± 2.93	FAS: 89 / 18.19 ± 1.94 PPS: 86 / 18.21 ± 1.97	FAS: 88 / 2.20 ± 2.79 / <0.001 / 1.61 ; 2.79 PPS: 85 / 2.24 ± 2.82 / <0.001 / 1.63 ; 2.85
ESS total score	Qualitative measure of daytime sleepiness and associated risks	FAS: 109 / 9.64 ± 5.56 PPS: 87 / 9.69 ± 5.72	FAS: 88 / 6.22 ± 4.12 PPS: 85 / 6.16 ± 4.15	FAS: 87 / -3.48 ± 4.30 / <0.001 / -4.40 ; -2.57 PPS: 84 / -3.50 ± 4.37 / <0.001 / -4.45 ; -2.55
Mean reduction in Apnea-Hypopnea Index (AHI) (events/hour)	Primary metric describing OSA severity	FAS: 110 / 28.00 ± 11.47 PPS: 88 / 27.79 ± 11.58	FAS: 89 / 9.52 ± 9.43 PPS: 88 / 9.52 ± 9.48	FAS: 89 / -18.29 ± 11.76 / <0.001 / -20.77 ; -15.81 PPS: 88 / -18.26 ± 11.83 / <0.001 / -20.77 ; -15.76

3. Subgroup Analyses

The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes (e.g. sex, age, race, BMI). In all subgroup analyses, except for the one based on race, there was a significant overlap in the confidence intervals of the various groups. This overlap confirms that there are no significant differences in treatment responses among the different subgroups. For the subgroup analysis done based on race, as there are very few subjects in two subgroups (Black or African American and Other), results should be interpreted cautiously.

Table 38 - Percentage of AHI and ODI at Month 12 for the various subgroups

Subgroups		**Percentage of Responders at Month 12 – Full Analysis Set (N=110) Worst Case Imputation**			
		n	n (%) of imputed missing values	Rate (n /N) of participants with 50% Reduction in AHI from baseline and AHI < 20 [95% CI]	Rate (n /N) of participants with 25% Reduction in ODI from baseline [95% CI]
Gender	**Male (N=78)**	78	16 (20.5%)	62.8% (49/78) [51.1% ; 73.5%]	71.8% (56/78) [60.5% ; 81.4%]
	Female (N=32)	32	5 (15.6%)	75.0% (24/32) [56.6% ; 88.5%]	81.3% (26/32) [63.6% ; 92.8%]
Age	**Age<52 (N=26)**	26	8 (30.8%)	53.8% (14/26) [33.4% ; 73.4%]	65.4% (17/26) [44.3% ; 82.8%]
	52≤Age≤62 (N=58)	58	10 (17.2%)	72.4% (42/58) [59.1% ; 83.3%]	79.3% (46/58) [66.6% ; 88.8%]
Race	**White (N=104)**	104	21 (20.2%)	64.4% (67/104) [54.4% ; 73.6%]	73.1% (76/104) [63.5% ; 81.3%]
	Black or African American (N=4)	4	0 (0.0%)	100.0% (4/4) [39.8% ; 100.0%]	100.0% (4/4) [39.8% ; 100.0%]
	Other (N=2)	2	0 (0.0%)	100.0% (2/2) [15.8% ; 100.0%]	100.0% (2/2) [15.8% ; 100.0%]
BMI	**BMI≤25 (N=15)**	15	4 (26.7%)	66.7% (10/15) [38.4% ; 88.2%]	66.7% (10/15) [38.4% ; 88.2%]
	25<BMI≤28 (N=34)	34	5 (14.7%)	73.5% (25/34) [55.6% ; 87.1%]	85.3% (29/34) [68.9% ; 95.0%]
	28<BMI≤30 (N=27)	27	5 (18.5%)	59.3% (16/27) [38.8% ; 77.6%]	70.4% (19/27) [49.8% ; 86.2%]
	30<BMI≤32 (N=30)	30	7 (23.3%)	63.3% (19/30) [43.9% ; 80.1%]	70.0% (21/30) [50.6% ; 85.3%]
	BMI>32 (N=4)	4	0 (0.0%)	75.0% (3/4) [19.4% ; 99.4%]	75.0% (3/4) [19.4% ; 99.4%]

4. Pediatric Extrapolation

Implantation in this patient population has not been studied and therefore is not recommended in patients less than 22 years of age. Existing clinical data was also not leveraged to support approval of a pediatric patient population.

XI. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 68 investigators of which none were full-time or part-time employees of the sponsor, and two (2) investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a, b, c and f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None
- Significant payment of other sorts: Two investigators ($49,680.40 USD and $119,354.63 USD).
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: None

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Results for additional performance outcomes were analyzed for significance using data from the DREAM study.

Total Sleep Time and Total Events

Total Sleep Time
On average, subjects slept a little over 6 hours at both Baseline and Month 12 PSGs. Total sleep time (TST) at Baseline (367.3±54.3 mins, n=110) and Month 12 (362.8±54.3 mins, n=89) were not significantly different (p=0.962).

Total Events
Significant decrease in the total apneas, obstructive apneas and hypopneas were observed at Month 12 PSG compared to the Baseline values ($p<0.001$). While the absolute value of hypopneas saw the greatest decrease (65.2±56.5 events/night) compared to the obstructive

apneas (44.0±51.6 events/night), the apneas had a higher proportion of decrease at Month 12 PSG (75% vs 65%) (Figure 17).

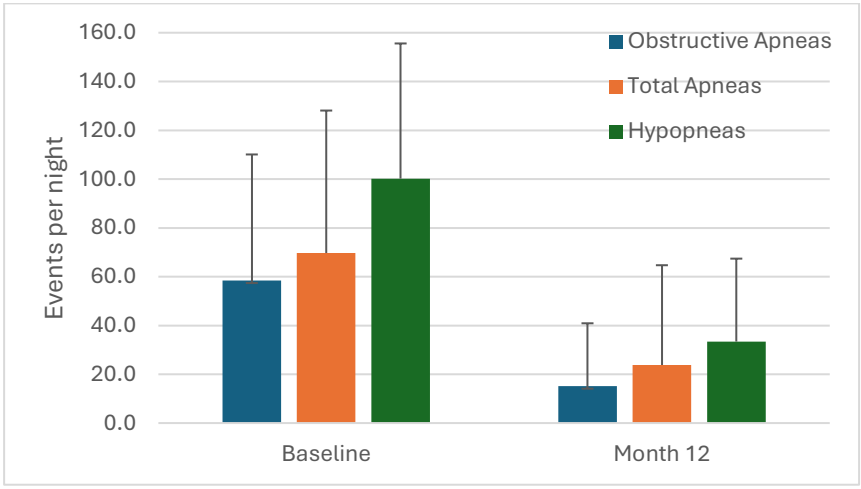

Figure 17: Changes in Obstructive and Total Apneas and Hypopneas

Improvement in supine and non-supine AHI

Changes in Sleep Position Specific Events

A significant decrease in both total events and events per hour (AHI) was observed at Month 12 PSG compared to the Baseline PSG. Specifically, events in non-supine and supine sleep positions at Baseline (45.3±47.2 events and 124.5±51.9 events, respectively; n=110) saw significant reduction at Month 12 PSG (22.3±39.5 and 34.9±27.6 events, respectively; n=89, p<0.001) (Figure 18).

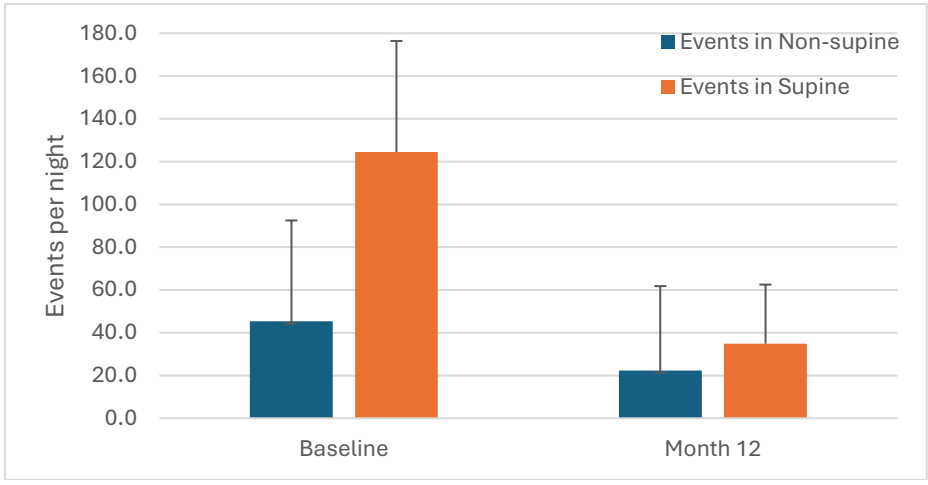

Figure 18: Number of events in non-supine and supine position at Baseline and Month 12 PSGs.

As seen from Figure 19, the improvement was also reflected in the (apnea-hypopnea) indices - 12.7±12.8 events/hr and 48.9±19.6 events/hr, in non-supine and supine positions, respectively (n=110) reduced to 5.2±8.2 events/hr and 22.7±19.9 events/hr (n=89, p<0.001). In summary, the median AHI improvement in the entire patient population (70.8%) is similar to those observed in supine (66.6%) and in non-supine (71.0%) sleep positions.

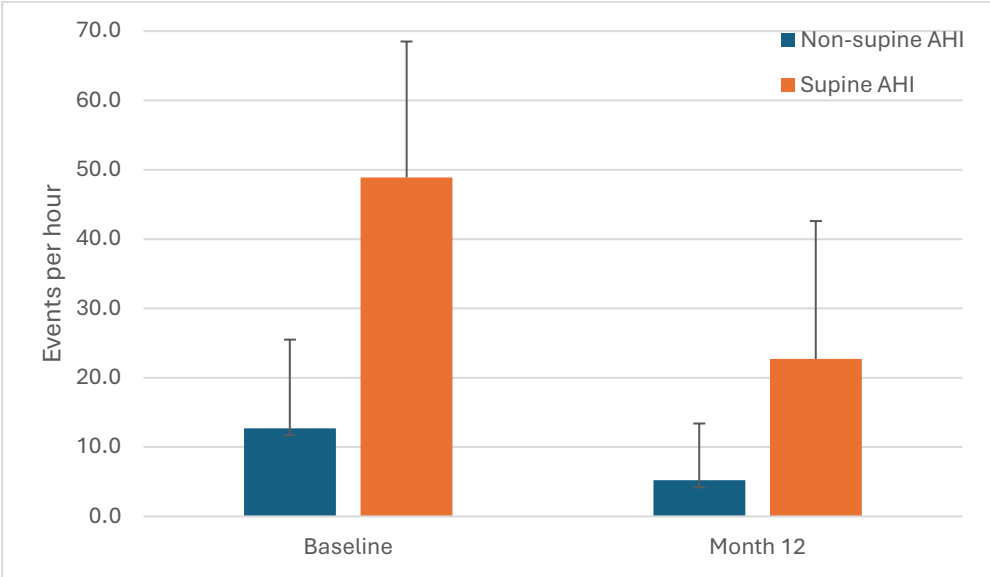

Figure 19: Non-supine and supine AHI at Baseline and Month 12 PSGs.

At Month 12, assessing responders in supine OSA symptoms, at least 66.3% of subjects report at least 50% improvements. Nearly 51% and 45% of them meet the Sher criteria and modified Sher criteria, respectively (Table 39). In those subjects with positional OSA (supine AHI≥2x non-supine AHI), identical improvements were observed.

Table 39: Supine AHI responders at M12

		All M12 Completers	Those with positional OSA
Subjects with > 50% improvement	n	89	78
	Yes	**59 (66.3%)**	**53 (67.9%)**
	No	30 (33.7%)	25 (32.1%)
Sher Criteria: Subjects with at least 50% reduction in supine AHI from baseline* and supine AHI < 20	**Yes**	**45 (50.6%)**	**40 (51.3%)**
	No	44 (49.4%)	38 (48.7%)
Modified Sher Criteria: Subjects with at least 50% reduction in supine AHI from baseline* and supine AHI < 15	**Yes**	**40 (44.9%)**	**36 (46.2%)**
	No	49 (55.1%)	42 (53.8%)

Table 40: Supine AHI Scores and Responder Status Segmented by Severity

OSA Severity	Mean Baseline Score (events/hr)	Mean M12 Score (events/hr)	Proportion of Subjects	
			≥50% improvement (95% CI)	Sher responders (95% CI)
Moderate (15<AHI≤30, n=15)	22.7±3.3	8.1±6.5	73.3% (44.9%, 92.2%)	73.3% (44.9%, 92.2%)
Severe (30<AHI≤65, n=50)	47.2±11.5	23.2±20.3	62.0% (47.2%, 75.4%)	54.0% (39.3%, 68.2%)
AHI>65 (n=22)	75.9±9.5	32.8±19.5	72.7% (49.8%, 89.3%)	27.3% (10.7%, 50.2%)

AHI at M12

Distribution of AHI for subjects (number & percent) at M12 PSG are listed below.

- AHI<20 – 80/89 (89.9%)
- AHI<15 – 73/89 (82.0%)
- AHI<10 – 60/89 (67.4%)
- AHI<5 – 31/89 (34.8%)

Over 80% of the patients had their AHI resolved to mild symptoms while 35% of them became asymptomatic post-Genio therapy.

Therapy Effect on Snoring

Subjects were asked to assess how their bed partner scored their snoring intensity on a categorical scale (no snoring, soft snoring, loud snoring, very loud snoring, or bed partner/subject leaves room). Table 41 provides the percentage of subjects in each category at baseline (N=85) and at the 12-month visit (N=69) for the 93 subjects that reached the 12-month visit. The reason why some subjects do not appear in the baseline or 12-month data is that they either did not have a bed partner or did not share a room. The percentage of bed partners reporting no- or soft snoring increased from 16.5% at baseline to 69.6% at the 12-month visit.

Table 41: Snoring Scoring Report at Baseline vs 12-Month Visit

Snoring scale	Baseline (N=85)	12-Month Visit (N=69)
No snoring	5 (5.9%)	12 (17.4%)
Soft snoring	9 (10.6%)	36 (52.2%)
Loud snoring	21 (24.7%)	15 (21.7%)
Very loud snoring	30 (35.3%)	2 (2.9%)
Bed partner/subject leaves room	20 (23.5%)	4 (5.8%)

Genio® System Usage at the Month 12 Visit

Nightly usage of the Genio® system was evaluated through a daily diary completed by the subjects to assess the number of hours used per night and the number of nights used per week.

Preceding the 12-month visit, 59 out of the 70 (84.3%) subjects who had completed the diary, reported using the Genio® system at least 70% of the nights with a nightly use of more than 4 hours. The device was used over 70% of the nights by 85.9% (61/71) of the subjects and 97.1% (68/70) of the subjects reported using the Genio® system for at least 4 hours a night. The mean usage was 6.24 ± 1.20 hours per night.

As a reference, CPAP use of 4 hours/night on 70% of nights was generally established as a clinical and empiric benchmark of CPAP adherence.

Subject Satisfaction at the Month 12 Visit

Overall subject satisfaction with the Genio® system was assessed using a categorical Likert scale (extremely satisfied, somewhat satisfied, somewhat dissatisfied, or extremely dissatisfied) in 88 subjects that completed questionnaire at the 12-month visit. Three subjects did not complete the questionnaire at the 12-month visit. As shown in Table 42, 79 out of 88 subjects (89.8%) were extremely or somewhat satisfied with their Genio® system. Only 9 (10.2%) subjects were dissatisfied due to residual snoring or discomfort.

Table 42: Overall Satisfaction Level of Subjects at 12-Month Visit – FAS (N=110)

Overall Satisfaction Level	12-Month Visit n (%)
n	88
Extremely satisfied	51 (58.0%)
Somewhat satisfied	28 (31.8%)
Somewhat dissatisfied	8 (9.1%)
Extremely dissatisfied	1 (1.1%)

Surgeon training

The surgical procedure was performed by ENT surgeons using standard surgical techniques. Surgeons received training on implant-specific techniques through didactic device presentations and cadaver implant sessions prior to performing their first implant procedure. The mean surgery time reported during the study was 2.37 ± 0.83 hours, and most subjects were discharged on the same day. Device programming and therapy titration were performed during clinic visits or in-lab polysomnography studies.

Safety and Effectiveness Data from OUS Post-market Clinical Follow-up Study (EliSA)

Upon CE Mark approval of the Genio® System, Nyxoah initiated the EliSA trial, a post market clinical follow up (PMCF) study. The purpose of this study is to assess the long-term safety and performance of the Genio® System and to identify any potential new risks not previously encountered during the pivotal study. Data was collected under normal conditions of use.

The EliSA study includes collection of performance related data (e.g., change of AHI, change of

ODI, etc.) as well as safety data (collection of adverse events and device deficiencies). The primary and secondary outcomes for the EliSA study differ from those used for the DREAM study (i.e., change in AHI vs. responder rates). Additionally, the inclusion and exclusion criteria in EliSA allows for the enrollment of patients more severe OSA symptoms (higher mean AHI with fewer restrictions on co-morbidities or exclusionary medications) and those with a higher BMI level than what was allowed in the DREAM study.

The EliSA study aims to include 110 implanted patients with a 5-year follow-up period. As of December 12th, 2024, 101 patients have been implanted in Germany, the Netherlands, Belgium and Switzerland. The enrollment is still ongoing, and currently, only 57.3% (n=63) of the subjects have completed the month 12 follow-up. A total of six (6) SAEs and 184 AEs (183 confirmed by the CEC) have been reported.

The preliminary results from the EliSA study are provided in Table 43 below. The responder rate based on Sher criteria (Table 44) and the line plot showing baseline and final AHI (Figure 20) are also provided.

Table 43. EliSA preliminary AHI and ODI results for subjects completing month 12 follow-up

EliSA preliminary results	Screening (Mean±SD)	M12 (Mean±SD)	Mean change (Mean±SD)	% change (Mean±SD)
AHI (N=63)	36.1±14.2	24.7±17.1	-11.4±15.8	-30.5±40.1
ODI (N=62)	31.8±15.2	25.5±17.1	-6.3±15.9	-16.0±50.5

Table 44. EliSA preliminary responder rates for subjects completing month 12 follow-up

Responder Rates	
AHI Responder	41.3%
AHI Sher Responder	38.1%
ODI Responder	51.6%
AHI responder = 50% improvement from screening AHI Sher responder = 50% improvement + residual AHI < 20 ODI responder = 25% improvement from screening	

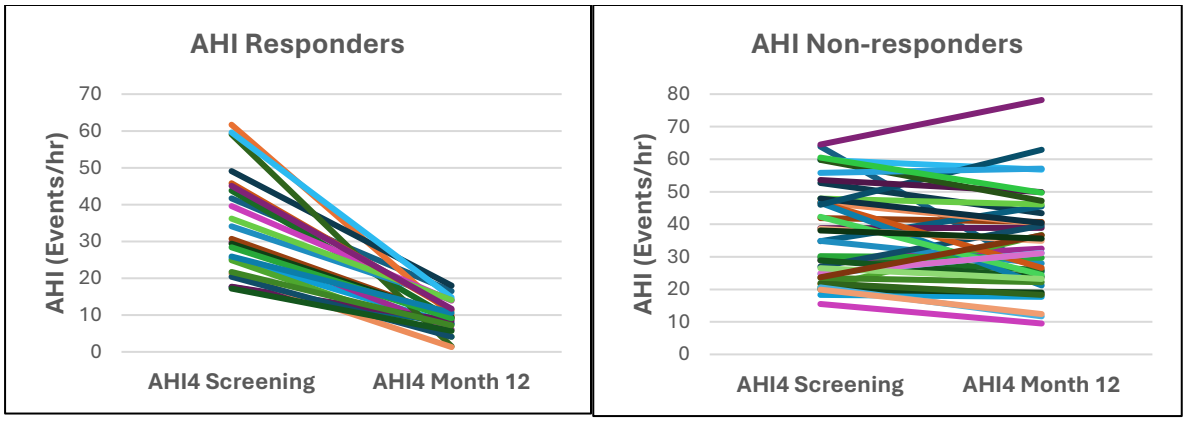

Figure 20. Line plot showing preliminary data for baseline and final AHI for EliSA study subjects (responders and non-responders) completing month 12 follow-up

The data presented for the EliSA study is preliminary as there was no planned interim analysis defined apriori in the study protocol. The study was conducted in a real-world setup where patients were afforded fewer (just one mandatory PSG) opportunities to be titrated to optimal therapy response through a full night PSG prior to their 12-month visit. Moreover, the titration algorithm of Genio® therapy has been refined since these patients were implanted as witnessed by the improvement in responder rate in the DREAM study.

Limited Data on OSA Patients with Complete Concentric Collapse (CCC)

Nyxoah has implanted OSA patients with CCC of the soft palate and collected real-world data from Europe (where CCC is on label use). Data from thirteen implanted patients with follow-up data was analyzed. Mean AHI (±SD) and follow-up time were 39.1±18.0 events/hr. and 20.7±9.2 months, respectively. Range of AHI and follow-up time are 18-81 events/hr. and 5 to 38.3 months, respectively. A mean improvement of 62.6% (±23.0%) was observed in these 13 patients with nine (69.2%) of them meeting the Sher criteria (≥50% improvement in AHI and residual AHI <20 events/hr.). For these thirteen patients, no adverse events have been reported.

Additional clinical evidence comes from the BETTER SLEEP study, a prospective clinical trial designed to evaluate safety and performance in patients with and without CCC of the soft palate. Among the 42 implanted patients, 18 (42.9%) had CCC, and safety results showed no differential adverse event profile between CCC and non-CCC patients. For effectiveness, patients with CCC (N=8) who reached the 6-month endpoint achieved significant reductions in OSA severity, with mean AHI decreasing from 32.1 ± 10.0 events/h at baseline to 21.3 ± 21.0 events/h (mean reduction of 10.8 ± 15.8 events/h), and ODI decreasing from 27.3 ± 13.1 events/h to 17.4 ± 18.7 events/h (mean reduction of 9.9 ± 12.5 events/h). The AHI responder rate using Sher criteria was 62.5% (5/8) in CCC patients.

Due to the limited clinical data available for OSA patients with CCC, there is insufficient evidence to establish the indication of the Genio® System 2.1 and its safety and effectiveness in OSA Patients with CCC.

XIII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Anesthesiology and Respiratory Therapy Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

This 12-month multicenter study was initiated to evaluate the safety and efficacy of the Genio® System 2.1 in adult subjects who continue to struggle with moderate to severe OSA after they have failed first line therapies. The major findings from this study include:

- Both co-primary effectiveness endpoints were met, with >50% of participants achieving AHI4 responder criteria (≥50% reduction and AHI4 <20) and ODI4 responder criteria (≥25% reduction) at 12 months.
- All six secondary effectiveness endpoints were met including SNORE-25, oxygen saturation, ODI4, FOSQ-10 score, ESS, OSA severity from baseline to 12-months.
- Safety results with a 6.1% device-related and 5.2% implant procedure-related serious adverse event rate through 12 months post-implantation.

A. Safety Conclusions

The risks of the Genio® System 2.1 are based on data collected during a 12-month period post-surgery as part of the DREAM clinical study conducted to support PMA approval as described above.

Out of the 115 patients in whom implant was attempted, 85 (73.9%) experienced a total of 252 non-serious device and/or implant procedure-related AEs. The most common non-serious procedure-related AEs were difficulty swallowing/dysphagia (11.7% of patients) and incision site swelling (12.2% of patients). Among device-related non-serious events, local skin irritation from the Disposable Patch occurred in 24.3% of patients, while stimulation-related discomfort affected 14.8% and tongue discomfort occurred in 12.2% of patients.

There were 16 serious adverse events, of which 3 events (2.6%) were unrelated to the device/procedure, while 13 events (11.3%) were device and/or procedure-related. The device/procedure-related SAEs comprised 6 device-related events (5.2%), 6 procedure-related events (5.2%), and 1 event related to both device and procedure (0.9%), indicating a rate of 6.1% for device-related serious adverse events through 12 months post-implantation. The SAEs included 3 device migrations/extrusions requiring explantation, 2 cases of dysphagia, 1 incision site hematoma, 1 epistaxis, and 1 left bundle branch block. Additionally, 5 surgical interventions (1 repositioning, 4

replacement surgeries) were performed, with 2 successful replacements. The majority of SAEs and non-serious AEs resolved without sequelae.

Extended follow-up data through 24 months showed 13 total (11.3%) cases of repositionings, revisions and explants. Contributing factors included the surgical learning curve, early device migration prior to therapy activation, and extraneous mechanical events from procedures that may be unrelated to the therapy or device.

Risk mitigation strategies for the serious adverse events include enhanced physician training protocols, proctor support and certification, improved design features in the IS Model #2954 (flexible shoulder design, ceramic encapsulation), and comprehensive labeling with appropriate warnings and precautions.

B. Effectiveness Conclusions

The Genio® System demonstrated clinically and statistically significant effectiveness outcomes, with AHI4 responder rates of 66.4% (≥50% reduction and AHI4 <20) and ODI4 responder rates of 74.5% (≥25% reduction) at 12 months in the full analysis dataset. Both co-primary effectiveness endpoints exceeded the pre-specified performance goal of 50%, confirming the clinical benefit of bilateral hypoglossal nerve stimulation.

All six secondary effectiveness endpoints demonstrated clinically meaningful improvements from baseline to 12 months, including OSA-specific quality of life (SNORE-25), hypoxemic burden (percentage of sleep time with oxygen saturation <90%), intermittent hypoxia (ODI4), functional outcomes (FOSQ-10), daytime sleepiness (ESS), and overall OSA severity (AHI4). These comprehensive improvements indicate broad therapeutic benefit beyond primary efficacy measures.

The study successfully met both co-primary and all secondary effectiveness endpoints, with clinical benefits further supported by high patient satisfaction (89.8% of patients reported being satisfied at 12 months).

C. Benefit-Risk Determination

OSA is a sleep disorder characterized by recurrent airway narrowing or closures during sleep, which can result in severe complications if left untreated. These complications include neurobehavioral impairment, memory deficits, poor concentration, behavioral problems, cardiovascular comorbidities, reduced quality of life, metabolic disorders, and depression.

The most common first-line treatment for OSA is CPAP therapy. However, multiple CPAP clinical trials have demonstrated adherence rates of less than 50%, with the APPLES study showing only 39% of subjects remained compliant with CPAP therapy at 6 months after initial prescription [i]. Alternative therapies to CPAP are limited and include oral appliance therapy (e.g., mandibular advancement devices),

pharmacotherapy (e.g., tirzepatide for patients with comorbid obesity), and anatomical surgical treatments.

Each alternative treatment has significant limitations. Oral appliances are primarily indicated for mild-to-moderate OSA [ii], while the Agency for Healthcare Research and Quality has determined that clinical evidence for upper airway surgery efficacy is insufficient [iii]. Therefore, when the clinical needs of the OSA patient population are not met by currently available non-surgical standard-of-care treatments due to intolerance, ineligibility, or lack of effectiveness, the Genio® System provides a needed alternative treatment option.

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above.

The Genio® System has the following benefits:

- Reduction of OSA severity in patients intolerant of first-line therapies
- Clinically relevant improvement in OSA symptoms and quality of life
- Compliance to the Genio® System compared favorably to PAP treatment
- Improvement in supine and non-supine OSA symptoms
- Positive therapy effect on snoring
- Patient satisfaction associated with the Genio® System
- Improvement in time spent at SaO_2 <90%

Besides the study related benefits, the device design has the following benefits:

- Implant is a bilateral neurostimulator (potential benefit in supine sleep)
- Implanted via a single incision surgical procedure
- A passive implant with no sensing leads or battery that is powered and controlled by an external activation chip
- MR Conditional up to 3T

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above.

- Requires surgery
- Permanent implant if not explanted
- Risk of electrode migration
- Potential for revision, explant, or re-implantation surgery
- Risk of potential discomfort for the patient due to electrical stimulation
- Unnecessary intervention due to possibility of spontaneous remission of OSA

Common adverse events include:

- Local skin irritation
- Dysphagia
- Incision site swelling
- Medical device discomfort

Additional factors to be considered in determining probable risks and benefits for the Genio® System device included:

1. **Patient Perspective**
   Patient perspectives were assessed through validated instruments including the SNORE-25 questionnaire, which evaluated OSA-specific quality of life across five domains (sleep problems, awake problems, medical problems, emotional & personal problems, and occupational problems), and the FOSQ-10 questionnaire, which assessed the impact of excessive sleepiness on daily activities including activity level, vigilance, intimacy, general productivity, and social outcomes. Additionally, patients reported on therapy effects on snoring intensity using a categorical scale, and overall treatment satisfaction was measured using a 4-point Likert scale. Results demonstrated significant improvements in OSA-specific quality of life (SNORE-25 mean improvement of -1.02 ± 0.84, $p<0.001$), functional outcomes related to sleep disorders (FOSQ-10 mean improvement of 2.20 ± 2.79, $p<0.001$), reduced snoring intensity (69.6% of bed partners reported no or soft snoring at 12 months compared to 16.5% at baseline), and high patient satisfaction (89.8% of patients reported being extremely or somewhat satisfied with the Genio® System at 12 months).

2. **Treating OSA in both supine and non-supine conditions**
   Beyond improvement in the overall AHI, improvement in supine (position-dependent) and non-supine AHI was observed. Time spent below 90% blood oxygenation ($SaO_2<90\%$) also improved significantly, and nearly a third of the subjects completing the 12-month visit were deemed asymptomatic for OSA (AHI<5 events/hr).

3. **Impact on snoring**
   Snoring represents a significant impact on the bed partner of OSA patients. DREAM study demonstrated that roughly 70% of patients had improvement in snoring (soft or no snoring). CPAP, in comparison, generally provides consistent reduction in snoring but may trade the noise of snoring with noise generated by air leaks and general machine operation.

4. **MRI Compatibility**
   The Genio® System is considered 1.5T and 3T Magnetic Resonance Conditional. Current MRI scan limitations of unilateral hypoglossal nerve stimulators allow imaging only up to 1.5T. Given the prevalence of co-morbid conditions in the OSA patient population, the ability to obtain images with higher resolution and better quality (i.e., 3T scans) may be critical in diagnosis of disease conditions and positive health outcomes.

In conclusion, the available data support that for adult patients with moderate to severe Obstructive Sleep Apnea (OSA) (AHI 15-65 events/hour) who have failed, cannot tolerate, or are ineligible for standard-of-care treatments, the probable benefits of the Genio® System 2.1 outweigh the probable risks.

D. Overall Conclusions

The study results demonstrated clinically and statistically significant reductions in OSA severity, improvements in daily symptoms and OSA-related quality of life, with an acceptable incidence of adverse events. The study data also provided evidence of improvement in both supine and non-supine OSA symptoms, therapeutic effects on snoring, and high patient satisfaction associated with the Genio® System 2.1. Specifically, 66.4% of patients achieved the primary AHI responder criteria (≥50% reduction and AHI <20), 74.5% of patients met the ODI responder criteria (≥25% reduction), and 89.8% of patients reported being satisfied with treatment at 12 months. All secondary endpoints demonstrated statistically significant improvements, including comprehensive quality of life measures.

The study results indicate that a significant portion of the target patient population—adults with moderate to severe OSA who have failed, cannot tolerate, or are ineligible for standard-of-care treatments—can achieve clinically meaningful therapeutic outcomes. This addresses a substantial unmet medical need in OSA management where alternative treatment options are limited. Based on the comprehensive clinical and nonclinical data for the Genio® System 2.1, the probable benefits outweigh the probable risks in the targeted patient population.

XV. CDRH DECISION

CDRH issued an approval order on August 8, 2025. The final clinical conditions of approval cited in the approval order are described below.

1. **Extended Follow-up of the Premarket Cohort (DREAM Study):**
   This study will be conducted according to DREAM Clinical Investigational Plan Protocol Revision 8.0 dated March 26th, 2024. This is a prospective, single-arm cohort study designed to evaluate the long-term safety and efficacy of the Genio® system in 115 subjects previously implanted under the premarket study, with follow-up extending to 5 years post-surgery. The primary safety objective is to evaluate long-term device-related and procedure-related adverse events. The primary efficacy objectives include therapy efficacy measured by improvement in OSA severity (AHI4) and intermittent hypoxia (ODI4) using annual in-lab polysomnography at years 2, 3, 4, and 5, with success criteria defined as achieving a 50% responder rate for both AHI4 responder criteria (≥50% reduction and AHI4 <20) and ODI4 responder criteria (≥25% reduction). Secondary assessments include quality of life and functional outcomes through validated instruments (FOSQ-10, SNORE-25, Epworth Sleepiness Scale, hypoxemic burden, and EQ-5D-5L). All adverse events will be summarized by seriousness, severity, device relatedness, and temporal relationship to the procedure.

2. **New enrollment study (Post-Approval Study):** This study will be conducted according to CL-DREAMON-2024 Protocol dated March 12, 2025. This multicenter, prospective, single-arm, post-approval study aims to demonstrate the long-term safety and effectiveness of the Genio® System (IS Model #2954) in treating subjects diagnosed with moderate to severe obstructive sleep apnea (OSA) who are intolerant to or have failed/refused positive airway pressure (PAP) treatments. The study will include 229 subjects, with baseline visits followed by the implantation of the Genio® System, and therapy activation at 6 to 10 weeks post-implantation. Subjects will then have follow-up visits at 6 months, 9 months, 12 months, and every 6 months thereafter up to 5 years. Safety events, including device-related and procedure adverse events (AEs) and serious adverse events (SAEs) such as device explants due to infection, malfunction, or repositioning requiring surgery, will be captured at all scheduled and unscheduled visits. The safety of the device will also be monitored with specific criteria, including maximum migration, explant, and revision rates, which will be set at ≤5%, ≤4%, and ≤6.6%, respectively. The primary efficacy objectives include therapy efficacy measured by improvement in OSA severity (AHI4) and intermittent hypoxia (ODI4) using annual in-lab polysomnography at years 1, 2, 3, 4, and 5, with success criteria defined as achieving a 50% responder rate for both AHI4 responder criteria (≥50% reduction and AHI4 <20) and ODI4 responder criteria (≥25% reduction). Secondary endpoints will include subject satisfaction, global impression of change, and OSA-related symptoms as measured by the Epworth Sleepiness Scale. With 80% statistical power and a 2.5% level of significance, the study aims to reject the null hypotheses that the percentage of responders at Month 60 will be less than 50%. This study will continue to follow participants for up to 5 years, with endpoints assessed and reported yearly till the 60-month mark.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XVI. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVII. REFERENCES

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