# DE NOVO CLASSIFICATION REQUEST FOR NTX100 TONIC MOTOR ACTIVATION (NTX100 TOMAC) SYSTEM®

## REGULATORY INFORMATION

FDA identifies this generic type of device as:

**External lower extremity nerve stimulator for Restless Legs Syndrome**. An external lower extremity nerve stimulator for Restless Legs Syndrome is a prescription device that uses external electrical stimulators and cutaneous electrodes to stimulate nerves in the lower extremity (e.g., peroneal nerves) and evoke tonic, sustained muscle activation in the legs to reduce the symptoms of Restless Legs Syndrome.

**NEW REGULATION NUMBER:** 21 CFR 882.5887

**CLASSIFICATION:** Class II

**PRODUCT CODE:** QWD

## BACKGROUND

**DEVICE NAME:** NTX100 Tonic Motor Activation (NTX100 ToMAc) System®

**SUBMISSION NUMBER:** DEN220059

**DATE DE NOVO RECEIVED:** September 21, 2022

**SPONSOR INFORMATION:**

Noctrix Health, Inc.
6700 Koll Center Pkwy, Ste 310
Pleasanton, CA 94566

## INDICATIONS FOR USE

The NTX100 Tonic Motor Activation (ToMAc) System® is intended to reduce symptoms of primary moderate-severe Restless Legs Syndrome (RLS) and to improve sleep quality in adults refractory to medications.

## LIMITATIONS

The sale, distribution, and use of the NTX100 Tonic Motor Activation (ToMAc) System® are restricted to prescription use in accordance with 21 CFR 801.109.

The primary and key secondary efficacy endpoints were evaluated at 4 weeks of the clinical study. Therefore, long-term durability of the therapeutic effects of the NTX100 ToMAc System® has not been assessed.

The device is contraindicated for use by patients who have a cardiac pacemaker, implanted defibrillator, other implanted electronic device, or implanted metal near the device, because this may cause electric shock, burns, electrical interference, or death.

The stimulation electrodes should not be placed across or through the head, directly on the eyes, covering the mouth, on the front of the neck, on the chest or upper back, or crossing the heart.

The device cannot be used while driving, operating machinery, or during any activity in which electrical stimulation can put the patient at risk of injury.

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

## DEVICE DESCRIPTION

The NTX100 Tonic Motor Activation (ToMAc) System® is a non-surgical, non-implantable prescription device intended for the application of low-amplitude electrical stimulation to the common peroneal nerve at lateral side of the knees to reduce symptoms of moderate-severe Restless Legs Syndrome (RLS). Patients will be instructed to use the NTX100 ToMAc System® as needed for symptom relief for up to 120 minutes per 24-hour period.

The primary components of the NTX100 ToMAc System® include:

- Therapy Unit
- Charge Dispersing Interface (CDI)
- Charging accessories
- Clinician App (for clinician use only)
- Clinician Computer (for clinician use only)

An image of the NTX100 ToMAc System® is provided in **Figure 1**.

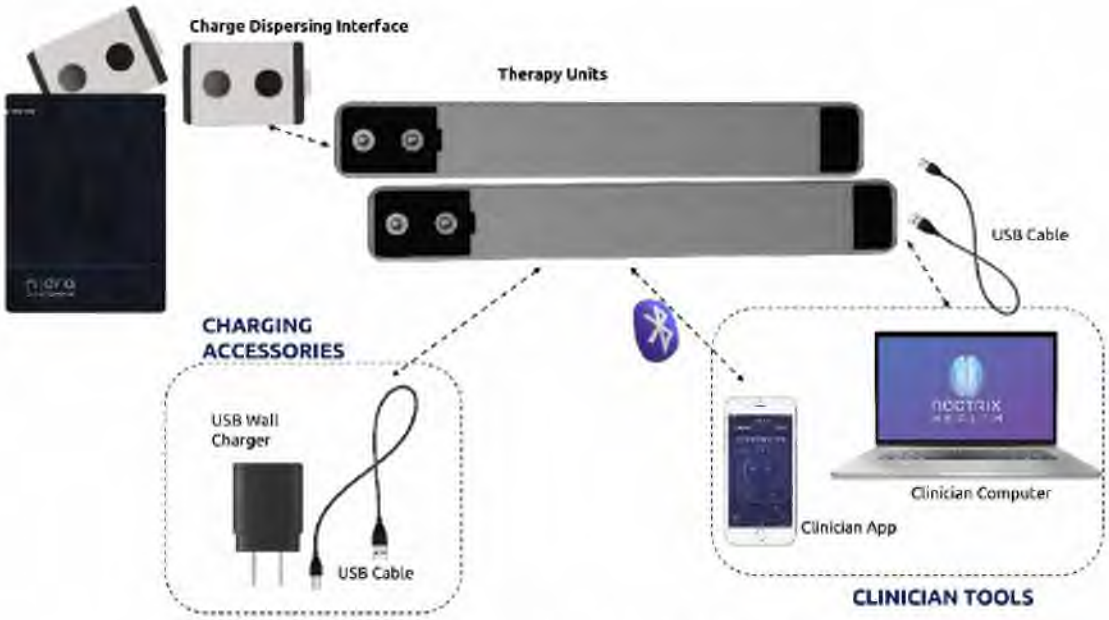


**Figure 1. NTX 100 Tonic Motor Activation (NTX100 ToMAc) System**

A. Therapy Unit

Each NTX100 ToMAc System® includes two therapy units intended to be used bi-laterally: one therapy unit worn under each knee, interfacing with the common peroneal nerves. The therapy unit is an assembly of electronics, rechargeable battery, and compressive conduction garment. The provided two therapy units can function independently. Individual calibration of the two therapy units is necessary and can result in different therapy settings for the unit worn on the left vs. the right leg. The therapy units have a simple user-interface that is used to turn ON/OFF, adjust intensity, or read status during therapy or charging sessions.

B. Charge Dispersing Interface (CDI)

The CDIs are disposable, adhesive, pre-spaced, hydrogel-coated electrodes intended to evenly disperse the output current generated by the therapy units over the targeted skin surface. The CDIs connect to the therapy units via stainless steel rivets and are intended to be used on both Therapy Units. The NTX100 ToMAc System® is designed to be used only with the Noctrix Health CDIs. Patients are instructed to replace the Noctrix Health CDIs on a weekly basis.

C. Charging Accessories

Each therapy unit is intended to be recharged via one supplied USB charging cable, that plugs into an AC adapter for US use (110V).

D. Clinician App

The Clinician App is pre-installed on a Noctrix Health-provided iOS device made available to each clinic. The application (iOS App) connects via a wireless, Bluetooth link to each therapy unit and allows the clinician to program custom therapy output settings that are specific to each patient. The Clinician App is used exclusively in the clinic and by the

clinician. Patients do not have access to this App. Patients do not have any wireless mechanism to communicate with the Therapy Unit or alter its settings.

E. Clinician Computer

The Clinician Computer includes pre-installed software that allows for the clinician to connect via USB to the therapy unit and download device-related log information from them. This wired connection may be used by the clinician to either troubleshoot or to provide feedback to patients based on their compliance with therapy. The computer also provides a mechanism for clinicians to securely transfer any log data to a cloud server via HTTPS. Instructions for using the pre-installed software and compatible computers for using the software are included in the Physician Guide.

F. Stimulation Parameters

The NTX100 ToMAc System® has a single output mode consisting of bi-phasic, charge balanced, current-controlled stimulation at a fixed frequency of 4,000 Hz. The technical specifications are listed in **Table 1**.

**Table 1. NTX100 ToMAc System® Output Parameters**

| Specification | Value |
|---|---|
| Waveform Shape | Bi-phasic pulsed, charge-balanced, rectangular |
| Regulated Current or Voltage | Current |
| Maximum Output Voltage (Volts) (+/- 5%) | 20 V @ 500 Ω<br>60 V @ 2000 Ω<br>60 V @ 10000 Ω |
| Maximum Output Current (mA) (+/- 10%) | 40 mA @ 500 Ω<br>30 mA @ 2000 Ω<br>6 mA @ 10000 Ω |
| Duration of primary (depolarizing) phase (µsec) | 125 µs |
| Pulse Duration (µsec) | 250 µs |
| Pulse Frequency (Hz) | 4,000 Hz |
| (b)(4) | |
| ON Time (minutes) | 30-minutes |
| Additional Features (specify, if applicable) | Automatic shut-off after 30- minute therapy session |

* Maximum Current Density and Average Power Density are computed for a single charge dispersing interface.

## SUMMARY OF NONCLINICAL/BENCH STUDIES

### BIOCOMPATIBILITY/MATERIALS

Tissue contacting components include the therapy unit leg bands and the CDIs. Per ISO 10993-1:2009 "*Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*," all patient contacting components are considered surface devices with intact skin contact with long-term (> 30 days) contact duration. The patient contacting components for the NTX100 ToMAc System® were found to be biocompatible based on evaluations for cytotoxicity, irritation, and sensitization per ISO 10993-1:2009 "*Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*."

### SHELF LIFE AND STERILITY

The NTX100 ToMAc System® does not have a shelf-life specification. The CDIs have a shelf-life of 12 months based on accelerated and actual age testing.

There are no sterilization requirements for the NTX100 ToMAc System®. The user does not sterilize the device before first or repeat uses. The CDI is non-sterile and designed for multiple single-patient use. They are intended to be replaced weekly and should not be cleaned. The therapy unit is reusable.

Cleaning and maintenance instructions for the NTX100 ToMAc System® have been provided in the labeling.

### ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The NTX100 ToMAc System® was tested according to the following FDA-recognized consensus standards:

- IEC 60601-1-2:2014 Ed:4.0 (Equivalent to AAMI/ANSI/IEC 60601-1-2:2014) "Medical Electrical Equipment - Part 1-2: General Requirements for Basic Safety and Essential Performance-Collateral Standard: Electromagnetic disturbances - Requirements and Tests."
- AAMI/ANSI ES60601-1:2005/(R)2012 and A1:2012, C1:2009/(R)2012 and A2:2010/(R)2012 (Consolidated Text) "Medical Electrical Equipment; Part 1: General requirements for basic safety and essential performance" (IEC 60601-1:2005, MOD).
- IEC 60601-1-11:2020 Ed:2.1 "Medical electrical equipment Part 1-11: General requirements for basic safety and essential performance collateral standard - Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment."
- IEC 60601-2-10:2016 Ed:2.1 "Medical electrical equipment Part 2-10: Particular requirements for basic safety and essential performance of nerve and muscle stimulators."

### SOFTWARE

A failure or latent flaw in the software of the NTX100 ToMAc System® could indirectly result in minor injury to the patient or operator; therefore, the software of this device is

considered to have a "Moderate" level of concern. The submission contained all the elements of software documentation corresponding to a "Moderate" level of concern, as outlined in the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices", issued May 11, 2005 (Guidance for the Content of Premarket Submissions for Software Contained in Medical Deivces (fda.gov)). Adequate documentation describing the software, firmware, software specifications, architecture design, software development environment, traceability, revision level history, unresolved anomalies and cybersecurity provides the foundation that the software will operate in a manner as described in the specifications. A hazard analysis was performed to characterize software risks including device malfunction and measurement related errors. The submission included verification and validation (V&V) testing to address the potential hazards with satisfactory result.

## ADDITIONAL PERFORMANCE TESTING

The following additional non-clinical testing was performed:

- **Wireless Coexistence Testing**

  The Clinician App of the NTX100 ToMAc System® communicates wirelessly with the Therapy Unit using Bluetooth low energy (BLE). This wireless communication with the device is used solely by the clinician in the "Professional HealthCare Facility Environment". Wireless quality of service, wireless coexistence and communication security testing was conducted per the FDA Guidance Document "Radio Frequency Wireless Technology in Medical Devices", issued August 14, 2013 (Attachment E CDRH Final Guidance Cover Sheet (fda.gov)). The testing demonstrates the necessary level of service and performance needed for the Clinician App under simulated clinical conditions of use in a "Professional HealthCare Facility Environment".

- **Battery Testing**

  The battery is certified by its manufacturer to maintain at least 80% of the initial capacity following 300 full charge/discharge cycles. The safety of the NTX100 ToMAc battery was tested in accordance with IEC 62133-2:2017 "Secondary cells and batteries containing alkaline or other non-acid electrolytes – Safety requirements for portable sealed secondary lithium cells, and for batteries made from them, for use in portable applications - Part 2: Lithium systems."

- **Electrical Stimulation Output Characterization:**

  Testing was performed to characterize the stimulation output when the Therapy Unit and CDI are attached to clinically relevant loads. Results demonstrated that the system meets specifications.

- **Electrode Bench Testing:**

  The CDIs have been tested to assess the mechanical measurements, the design of the electrodes (and tolerances), the electrical characteristics (impedance and current distribution) of the electrodes under the expected worst-case conditions of normal

operation, and the capability to remain consistent interface impedance between the CDIs and the skin during the therapy session. Results demonstrated that the electrodes passed all testing.

- **Electromyography (EMG) Testing:**

  The NTX100 ToMAc System® is intended to activate afferent fibers of the common peroneal nerve in a specific manner which leads to tonic sustained afferent activation of the tibialis anterior muscle of the leg. Electromyography (EMG) testing was conducted to demonstrate that bilateral stimulation of the common peroneal nerves evokes sustained increases of muscle tone in the lower leg muscles associated with walking without generating jerky muscle twitches or distracting sensations that would interfere with the patient's sleep.

## SUMMARY OF CLINICAL INFORMATION

### A. Overview

This is a multi-center study designed to evaluate the NTX100 ToMAc system® treating patients with moderate-severe primary RLS symptoms in adults refractory to medications. It consisted of a 4-wk. prospective, randomized, sham-controlled, double-blinded phase (Phase 1) followed by a 4-wk. prospective, open-label phase (Phase 2) for a total of 8-wks. of follow-up. A total of 133 participants were enrolled and analyzed.

### B. Subject Selection

Inclusion Criteria

1. Subject has received a medical diagnosis of RLS.
2. Subject is refractory to RLS medication as defined by at least one prescription medication administered to treat RLS for one or more following reasons, as determined by the investigator:
   - Adverse effects associated with the medication are intolerable.
   - Patient exhibits symptoms of augmentation.
   - Efficacy has reduced to the point where an up titration would be needed to maintain a sufficient response to medication.
   - The patient lacks sufficient response to medication at the maximum approved or recommended dosage.
   - The patient lacks sufficient response to medication at the maximum tolerable dosage due to adverse effects.
3. Subject has moderate-severe RLS symptoms as defined by a score of 15 or greater points on IRLS (International Restless Legs Syndrome Study Group Rating Scale) over the week prior to study entry.
4. Subject has RLS symptoms 2 or more nights per week during the week prior to study entry as defined by a score of 2, 3, or 4 on IRLS question #7.
5. RLS symptoms are most significant in the subject's lower legs and/or feet.

6. RLS symptoms are most significant at bedtime, after bedtime, and/or in the 2 hours before bedtime.
7. RLS symptoms between 10am and 6pm are not severe.
8. Subject agrees to not change dosage or schedule of any medications that are known to impact RLS symptoms during the study, including RLS medications, antidepressants, sleep medications, or sedative antihistamines.
9. Subject agrees to not make major lifestyle changes during the study that would significantly affect bedtime, such as major changes to diet, exercise, or career.
10. Subject possesses the necessary equipment, internet/phone accessibility, and communication ability to complete electronic questionnaires and respond to electronic communications and phone calls from the research staff throughout the in-home portion of the study.
11. Subject is $\geq 22$ and $\leq 79$ years of age when written informed consent is obtained.
12. Subject has signed a valid, IRB-approved informed consent form, can understand the requirements of the study and instructions for device usage, and can converse in English.

Exclusion Criteria

1. Subject has RLS that is known to be caused by another diagnosed condition (i.e., secondary RLS).
2. Subject is taking an unstable or inconsistent dose or schedule of medication that is likely to impact RLS symptoms, such as antidepressants, sleep medications, or sedative antihistamines or has changed dosage within the past 30 days.
3. Subject has changed dose and schedule of RLS medications within the month prior to study entry or is otherwise on an inconsistent dose or schedule of RLS medications.
4. Subject has prior experience with neurostimulation devices developed by the study sponsor, has prior experience using neurostimulation devices to treat RLS symptoms, or intends to use a neurostimulation device other than the study device during the study period.
5. Subject was misdiagnosed with RLS, as determined by the investigator (e.g., actual diagnosis of Periodic Limb Movement Disorder (PLMD), arthritis, leg spasms or neuropathy without comorbid RLS).
6. Subject has a primary sleep disorder other than RLS that significantly interferes with sleep at the present time (e.g., obstructive sleep apnea stably controlled via CPAP would not be an exclusion).
7. Subject has active medical device implant anywhere in the body (including but not limited to pacemakers, spinal cord stimulators, deep brain stimulators) or metal implant at the site of study device electrode application.
8. Subject has severe peripheral neuropathy affecting the lower legs and/or subject has neuropathy and is unable to clearly distinguish between symptoms of neuropathy and symptoms of RLS.
9. Subject reports that bedtime is typically outside of 9 pm-3 am or reports that bedtime regularly varies by more than 4 hours, such as due to shift work.

10. On nights with no RLS symptoms (if any), subject reports typical sleep onset latency of > 60 minutes.
11. Subject has been diagnosed with one of the following conditions:
    - Epilepsy or other seizure disorder
    - Current, active or acute or chronic infection other than common cold
    - A malignancy within the past 5 years (not including basal or squamous cell skin cancer)
    - Stage 4-5 chronic kidney disease or renal failure
    - Severe movement disorder symptoms (Parkinson's disease, Huntington's disease, dyskinesia, dystonia)
    - Deep vein thrombosis
    - Multiple sclerosis
12. Subject has moderate or severe cognitive disorder or mental illness.
13. Subject has current diagnosis of iron-deficient anemia or history of iron-deficient anemia within the past year.
14. Subject has known allergy to device materials, electrode gel, polyurethane foam, or lycra (or severe previous reaction to medical adhesives or bandages).
15. Subject has severe edema affecting lower legs.
16. Subject has any of the following at or near the location of device application.
    - Acute injury
    - Cellulitis
    - Open sores
    - Other skin condition
17. Subject is on dialysis or anticipated to start dialysis while participating in the study.
18. During the NTX100 calibration process, which is identical for subjects in the active and sham arms, subject reports not feeling stimulation sensations up to an intensity of 30 mA, the subject finds stimulation intensities less than 15 mA to be uncomfortable or distracting, or the device does not properly fit the subject.
19. Subject has received another investigational device or drug within 30 days before study entry, is planning to receive another investigational device or drug during the study or is planning to change RLS medications during the study.
20. Subject has undergone a major surgery (excluding dental work) in the 30 days prior to study entry.
21. Subject is unable or unwilling to comply with study requirements.
22. Subject is pregnant or trying to become pregnant.

23. Subject has a medical condition not listed above that may affect validity of the study as determined by the investigator.
24. Subject has a medical condition not listed above that may put the subject at risk as determined by the investigator.

C. **Randomization and Blinding**

Following consent and enrollment, authorized site staff were provided with each subject's assigned study device kit number during the randomization process. Subjects were randomized in a 1:1 allocation to either:

- NTX100 programmed to ACTIVE mode
- NTX100 programmed to SHAM mode

Randomization assignments were stratified by study center with randomly chosen block sizes of 4 or 6. Small but randomly determined block sizes preserve treatment assignment balance within study center while maintaining assignment unpredictability.

Blinding was assessed at the end of the randomized phase of the study (Evaluation 6, Week 4). Blinding was assessed in a 2x3 format such that subjects were asked to guess if they had received "Treatment", "Sham" or "Don't Know". Subjects who guessed "Treatment" or "Sham" were presented with a follow-up question where they were asked to select a primary reason for their guess between the following options: "Relief of RLS symptoms", "Side-effects", "Lack of Relief of RLS symptoms", or "Other." The purpose of this follow-up question was to determine whether correct guesses were due to preventable causes – such as a sham device that did not appear to be functional – or non-preventable causes – such as readily perceptible differences in therapeutic efficacy between active and sham.

D. **Intervention**

Following randomization, subjects were trained on proper usage of the device, including positioning of the devices on their legs. Instrument(s) designed for marking the human skin (body-marking pen) were employed to mark the locations of electrode placement. Device calibration was adjusted during device training based on subjective feedback from the subject.

Study subjects were instructed to self-administer treatment nightly as needed – typically after RLS symptoms start and before RLS symptoms became severe. The instructions for timing of device use could be adjusted based on the timing of RLS symptoms experienced by the subject. Once activated, a single session of treatment could run for approximately 30 minutes and then turn off automatically. Up to 120 total minutes per night could be used. If device battery life limited the number of uses per night, the following two timings of use could be prioritized: (1) at bedtime, to reduce symptoms and thus help with sleep initiation, and (2) when waking up in the middle of the night, to reduce symptoms and thus help with sleep re-initiation. Device intensity was typically set to the calibrated levels, but intensity could be increased if RLS symptoms are especially severe or decreased such as if RLS symptoms are mild.

Active and sham devices were physically identical and provided identical visual feedback during operation. Both active and sham mode delivered an initial ramp-up in stimulation intensity lasting approximately 30 seconds and during which sensations are typically

noticeable. No subjects with prior neurostimulation experience with NTX100 were enrolled.

E. **Study Endpoints:**

Safety:

The safety endpoints included a descriptive analysis of adverse events (AEs) for both study arms, classified and tabulated by seriousness, relationship to the device, and severity.

Effectiveness:

The clinical study included one pre-specified primary effectiveness measure and seven pre-specified secondary effectiveness measures as shown in **Table 2**.

**Table 2. Pre-specified primary and secondary effectiveness measures**

| **Primary** |
|---|
| The primary outcome measure was responder rate on the CGI-I (Clinical Global Impressions-Improvement) scale at Week 4 of Phase 1 relative to Baseline and compared between the study arms. Responder rate for the 7-point CGI-I scale was defined as the proportion of responses of "Much Improved" or "Very Much Improved". |
| **Secondary** |
| 1. PGI-I (Patient Global Impressions-Improvement) responder rate (defined as for CGI-I) at Week 4 relative to Baseline and compared between study arms.<br>2. Mean reduction in IRLS (International Restless Legs Syndrome Study Group Rating Scale) score at Week 4 relative to Baseline and compared between study arms.<br>3. Mean reduction in MOS-I (Medical outcomes Study Sleep Problems Index I) score at Week 4 relative to Baseline and compared between study arms.<br>4. Mean reduction in MOS-II (Medical outcomes Study Sleep Problems Index II) score at Week 4 relative to Baseline and compared between study arms.<br>5. Mean CGI-I score at Week 4 relative to Baseline and compared between study arms.<br>6. For subjects assigned to NTX100 in both Phases 1 and 2, reduction in IRLS Question #7 score ("How often do you get RLS symptoms?") from Baseline to Week 8. |

F. **Statistical Analysis**

The Statistical Analysis Plan (SAP) was developed in cooperation with an Independent Statistician and was finalized prior to breaking the study blinding.

The Intention-to-Treat (ITT) Population was used for the primary analysis of all efficacy endpoints. The PP (Per Protocol) population was used for a secondary analysis of all efficacy endpoints. The primary efficacy endpoint was the response on the Clinical Global Impressions-Improvement (CGI-I) scale at Week 4 of Phase 1 relative to Baseline (study entry) where a "successful" response was defined as a response of "Much Improved" or "Very Much Improved". This endpoint was summarized by treatment group using frequencies and percentages. The null and alternative hypotheses for this endpoint were as follows:

$H_0$: $RR_T \leq RR_S$

$H_1$: $RR_T > RR_S$

where $RR_T$ and $RR_S$ are the true responder rates for the treatment group and the sham control group, respectively. The null hypothesis was tested using a one-sided normal approximation test for the comparison of two proportions at the alpha = 0.025 level. Multiple imputation (MI) methods were used to impute any missing data.

## G. Results

### Demographics

The demographics for each study arm are shown in **Table 3**.

**Table 3. Demographics**

| Variable | Statistic | NTX100 (N=68) n (%) | Sham (N=65) n (%) |
|---|---|---|---|
| Age (years) | n | 68 | 65 |
| | Mean | 56.3 | 58.6 |
| | Median | 56.4 | 60.5 |
| | SD | 10.96 | 11.81 |
| | Min - Max | 31 - 77 | 29 - 79 |
| Sex (at birth) | | | |
| Male | n (%) | 29 (42.6) | 24 (36.9) |
| Female | n (%) | 39 (57.4) | 41 (63.1) |
| Ethnicity | | | |
| Hispanic or Latino | n (%) | 4 ( 5.9) | 4 ( 6.2) |
| Not Hispanic or Latino | n (%) | 64 (94.1) | 61 (93.8) |
| Race | | | |
| American Indian or Alaska Native | n (%) | 0 | 0 |
| Asian | n (%) | 2 ( 2.9) | 0 |
| Black or African American | n (%) | 2 ( 2.9) | 0 |
| Native Hawaiian or Pacific Islander | n (%) | 0 | 0 |
| White | n (%) | 64 (94.1) | 65 (100.0) |

### Blinding Assessment

The blinding assessment showed 53.8% of the active treatment group correctly identified they were receiving active treatment and 63.5% of the sham group correctly identified they were receiving sham treatment. For subjects assigned to NTX100, 86.4% of guesses were based on "Relief of RLS symptoms" (65.9%) or "Lack of Relief of RLS symptoms" (20.5%). For subjects assigned to Sham, 84.0% of guesses were based on "Relief of RLS symptoms" (20.0%) or "Lack of Relief of RLS symptoms" (64.0%).

Safety Endpoint

None of the individual study sites were terminated as part of the trial. A total of 2 serious adverse events (SAEs) occurred over the course of the trial. Neither of the two SAEs were related to the study device. Device-related AEs were typically mild and resolved rapidly with minimal or no follow-up. There were 89 device-related AEs affecting 50 subjects (37.6% of the safety analysis population), 88 of which were Mild, 1 was Moderate (limb discomfort). Of the 50 affected subjects, only 1 subject withdrew due to a device-related AE (07-017, AE was deemed possibly related and was described as knee pain and swelling) and another subject paused device use for 5 days but did not drop out; none of the other 48 (96%) paused device usage. The average time to resolve device-related AEs was 2.7 days, 72% of AEs resolved within 1 day or less, and 100% of AEs resolved. Device-related AEs resolved with minimal intervention; the most common actions taken were no action (57%), adjustment of Treatment stimulation intensity (13%), and adjustment of treatment positioning (11%). No medications were prescribed for device-related AEs. Most device-related AEs were administration site reactions; the most common categories were administration site discomfort (49%), administration site irritation (19%), or a temporary increase in symptoms related to RLS (25%).

Primary Effectiveness Outcome

The primary efficacy endpoint results demonstrate that, in the ITT population, the NTX100 Cohort had a CGI-I Responder Rate at 4 weeks that was significantly greater than that of the Sham cohort (44.6% versus 16.2%, p=0.0002; CI: [32.5, 56.8] versus [7.1, 25.2]).

**Table 4. Primary Efficacy Endpoint (CGI-I Responder Rate at Week 4) – (ITT Population)**

| Variable | NTX100 (N=68) n (%) | Sham (N=65) n (%) | p-value |
|---|---|---|---|
| CGI-I Responder at Week 4 | | | 0.0002 |
| Yes | 29 (44.6) | 10 (15.9) | |
| No | 36 (55.4) | 53 (84.1) | |
| Imputed CGI-I Responder Rate at Week 4 | | | 0.0001 |
| Responder Rate (%) | 44.6 | 16.2 | |
| 95% CI (%) | 32.5, 56.8 | 7.1, 25.2 | |

Secondary Effectiveness Endpoints

The results of secondary efficacy endpoints are provided in **Table 5** for the ITT population. Variables 1-6 in the tables were tested in that order and statistical testing was appropriate for a given variable only if the p-values were statistically significant (p-value

less than or equal to 0.025) for the previous variables. All p-values were statistically significant and thus all secondary endpoints were tested.

**Table 5. Key Secondary Efficacy Endpoints (ITT Population)**

| Variable | Statistic | NTX100 (N=68) | Sham (N=65) | p-value |
|---|---|---|---|---|
| 1. PGI-I Responder at Week 4 | | | | <0.0001 |
| Yes | n (%) | 33 (50.8) | 12 (19.0) | |
| No | n (%) | 32 (49.2) | 51 (81.0) | |
| 2. Reduction in Total IRLS score from Baseline to Week 4 | n | 65 | 63 | 0.0009 |
| | Mean | 7.2 | 3.8 | |
| | Median | 6.0 | 3.0 | |
| | SD | 6.16 | 5.91 | |
| | Min - Max | -3 - 23 | -11 - 20 | |
| 3. Reduction in MOS-II score from Baseline to Week 4 | n | 65 | 63 | 0.0002 |
| | Mean | 13.7 | 4.0 | |
| | Median | 11.7 | 3.9 | |
| | SD | 14.94 | 14.75 | |
| | Min - Max | -13 - 61 | -32 - 38 | |
| 4. Reduction in MOS-I score from Baseline to Week 4 | n | 65 | 63 | 0.0004 |
| | Mean | 11.8 | 2.8 | |
| | Median | 10.0 | 3.3 | |
| | SD | 14.71 | 14.94 | |
| | Min - Max | -13 - 60 | -30 - 43 | |
| 5. CGI-I score at Week 4 | n | 65 | 63 | <0.0001 |
| | Mean | 2.6 | 3.5 | |
| | Median | 3.0 | 4.0 | |
| | SD | 1.05 | 0.86 | |
| | Min - Max | 1 - 5 | 1 - 5 | |
| 6. Reduction in IRLS question #7 score from Baseline to Week 8 | n | 64 | - | <0.0001 |
| | Mean | 0.9 | - | |
| | Median | 1.0 | - | |
| | SD | 1.07 | - | |
| | Min - Max | -2 - 4 | - | |

## PEDIATRIC EXTRAPOLATION

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

## LABELING

The labeling is sufficient and satisfies the requirements of 21 CFR § 801.109 for a prescription device. The Instructions for Use are consistent with the clinical data and cover all the hazards and other clinically relevant information that may impact use of the NTX100 ToMAc System®. The labeling contains the Indications for Use, contraindications, warnings, precautions, device description, instructions for use and typical sensations experienced during treatment, a summary of the electrical stimulation output and device technical parameters, instructions on care and cleaning of the device, summary of clinical data, information related to electromagnetic compatibility and wireless specifications, device storage, disposal information, and symbols and markings.

## RISKS TO HEALTH

**Table 6** below identifies the risks to health that may be associated with use of the external lower extremity nerve stimulator for Restless Legs Syndrome and the measures necessary to mitigate these risks.

**Table 6. Identified Risks to Health and Mitigation Measures**

| Risks to Health | Mitigation Measures |
|---|---|
| Adverse tissue reaction | Biocompatibility evaluation |
| Skin discomfort, burns, electrical shock, or pain at stimulation site | Electromagnetic compatibility testing<br>Electrical, mechanical, and thermal safety testing<br>Non-clinical performance testing<br>Software verification, validation, and hazard analysis<br>Labeling |
| Worsening of Restless Legs Syndrome (RLS) symptoms, disrupted sleep | Non-clinical performance testing<br>Software verification, validation, and hazard analysis<br>Labeling |
| User error or device failure due to interference with other devices, leading to delayed or ineffective treatment | Electromagnetic compatibility (EMC) testing<br>Software verification, validation, and hazard analysis<br>Labeling |

## SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the external lower extremity nerve stimulator for Restless Legs Syndrome is subject to the following special controls:

(1) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. This testing must include:

   (i) Characterization of the electrical stimulation parameters, including the following: waveforms; output modes; maximum output voltage and maximum output current (at 500Ω, 2kΩ, and 10kΩ loads); pulse duration; frequency; net charge per pulse; maximum phase charge, maximum current density, maximum average current, and maximum average power density (at 500Ω);

   (ii) Characterization of the therapy output across sudden and rapid changes in load impedance; and

(iii) Characterization of electrode performance, including the electrical performance, adhesive integrity, shelf-life, reusability, and variation of impedance over the use of therapy.

(2) The tissue-contacting components of the device must be demonstrated to be biocompatible.

(3) Performance testing must demonstrate electrical, thermal, and mechanical safety along with electromagnetic compatibility (EMC) of the device in the intended use environment.

(4) Software verification, validation, and hazard analysis must be performed.

(5) Physician and patient labeling must include the following:

(i) Recommended treatment regimes, including frequency and duration of use, and identification of application site(s);

(ii) Typical sensations experienced during treatment;

(iii) Methods for identifying the appropriate stimulation intensity that is needed to reduce symptoms of Restless Legs Syndrome and is tolerable to patients;

(iv) A shelf life for the electrode and reuse information;

(v) Summaries of the electrical stimulation parameters and device technical parameters (including any wireless specifications); and

(vi) Instructions on how to maintain the device, including all user-interface components.

**BENEFIT/RISK DETERMINATION**

The randomized controlled trial demonstrated several clinically important benefits for the use of this device for reducing the symptoms of RLS in adults. Specifically, the active treatment group demonstrated:

• Statistically and clinically meaningful improvement in clinician assessed symptoms as measured by CGI-I responder rates (primary efficacy measure).

• Global patient impression of improvement over 4 weeks as measured by the PGI-I assessment showed significantly more responders in the active treatment compared to sham.

• Statistically significant improvement compared to sham in all additional secondary efficacy measures including reduction in total IRLS score, improvement in sleep quality scores (MOS-I, MOS-II), improvement in CGI-I mean scores, and reduction in frequency of RLS symptoms.

• Statistically significant improvement compared to sham in additional efficacy measures including reduction in trouble falling asleep and reduction in daytime sleepiness.

The trial met its primary effectiveness outcome of a significant difference as compared to sham in the 4-week CGI-I responder rates. Additionally, all secondary endpoints assessed indicated statistically significant improvement compared to the sham control. Additional examination of the patient satisfaction data also highlighted that 92% of patients would recommend the device to a friend or family member, and that 89% would continue to use the treatment.

The risks of the device are based on data collected in the randomized controlled trial. Specifically, there were no serious adverse events reported in the study and all adverse events were minor. The most common adverse event experienced when using the NTX100 ToMAc device to treat the symptoms of RLS was administration site discomfort or irritation, a common side-effect of electrical devices applied to the skin that typically resolves quickly with conservative measures. Based on this information the risk associated with the NTX100 ToMAc device is considered low.

Patient Perspectives

Upon completion of the study (Evaluation Visit 11) subjects were asked a series of questions regarding their satisfaction with the treatment and were asked for feedback on the device and treatment in general. 88.0% (112/126) and 96% (121/126) of the subjects responded "yes" to the question "would you like to continue using this treatment" and "would you like to be notified when this treatment becomes commercially available", respectively. The most common feedback received from the patients involved a request to make the charging port more accessible or charging easier in general (34.1%, 43/126) and to extend the battery life and/or allow for longer treatments between charges (23.8%, 30/126). Additional patient perspectives considered for the NTX100 ToMAc System® included patient reported outcomes (PROs) that assess patients' impression about the treatment effectiveness and disease impact, including the Clinical Global Impressions-Improvement (CGI-I), PGI-I (Patient Global Impressions-Improvement), and Medical Outcomes Study Sleep Problems Index.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for the NTX100 ToMAc System® device for the following indications for use statement:

> The NTX100 Tonic Motor Activation (ToMAc) System® is intended to reduce symptoms of primary moderate-severe Restless Legs Syndrome and to improve sleep quality in adults refractory to medications.

The NTX100 ToMAc System® provides benefits, and the risks can be mitigated by the use of general controls and the identified special controls.

## CONCLUSION

The De Novo request for the NTX100 ToMAc System® is granted and the device is classified under the following:

Product Code: QWD
Device Type: External lower extremity nerve stimulator for Restless Legs Syndrome
Class: II
Regulation: 21 CFR 882.5887