DE NOVO CLASSIFICATION REQUEST FOR QUELL-FIBROMYALGIA (QUELL-FM)

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Transcutaneous electrical nerve stimulator to treat fibromyalgia symptoms. A transcutaneous electrical nerve stimulator to treat fibromyalgia symptoms is a prescription device that transcutaneously stimulates a patient's sensory nerves through electrodes placed on the skin.

NEW REGULATION NUMBER: 21 CFR 882.5888

CLASSIFICATION: Class II

PRODUCT CODE: QSQ

BACKGROUND

DEVICE NAME: Quell-Fibromyalgia (Quell-FM)

SUBMISSION NUMBER: DEN210046

DATE OF DE NOVO: October 6, 2021

CONTACT: NeuroMetrix Inc.
4b Gill Street
Woburn, MA 01801

INDICATIONS FOR USE

The Quell-FM is a transcutaneous electrical nerve stimulation (TENS) device indicated as an aid for reducing the symptoms of fibromyalgia in adults with high pain sensitivity. The Quell-FM may be used during sleep. The Quell-FM is labeled for use only with compatible NeuroMetrix electrodes.

LIMITATIONS

The sale, distribution, and use of the Quell-FM are restricted to prescription use in accordance with 21 CFR 801.109.

Many participants in the clinical study were also taking medication for fibromyalgia and it was difficult to assess the effects of the device compared to medication.

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 MORE COMPLETE LIST OF CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS.

DEVICE DESCRIPTION

Quell-FM is a wearable, transcutaneous electrical nerve stimulator designed to stimulate sensory nerves in the upper-calf region. The device utilizes a microprocessor running embedded software and a custom high-voltage Application Specific Integrated Circuit (ASIC) to generate current regulated stimulating pulses with specific characteristics including pulse shape, amplitude, duration, pattern, and frequency. The device utilizes Bluetooth® low energy (BLE) to communicate with a mobile device that allows the user to start and stop therapy, control stimulation intensity, and modify certain operating characteristics. The device is powered by an embedded rechargeable lithium-ion polymer battery that is charged through a USB cable connected to an AC adapter. An image of the device and its placement on the upper calf is provided in **Figure 1**.

Figure 1. Quell-FM device and Band (A). Placement of device in Band and attachment of electrode (B). Placement of Quell-FM on upper calf (C).

The primary components of the device include the Quell-FM device, Band, Electrodes, and Quell-FM mobile app.

A. Quell-FM Device

The Quell-FM device delivers electrical stimulation to the user through a disposable electrode placed on the user's body. The Quell-FM is labeled for use only with compatible NeuroMetrix electrodes (previously cleared in K140586), to which it connects through insulated female medical snap connectors embedded within its housing; no lead-wires are used.

B. Band

A flexible band secures the Quell-FM device and the electrode to the user's leg using a hook and loop material.

C. Electrodes

The Quell-FM device is labeled for use only with compatible NeuroMetrix electrodes (i.e., electrodes cleared under K140586). This use specification, in part, ensures the safe use of the device during sleep because NeuroMetrix electrodes have a known surface area that allows the device to quantitively determine relative skin contact area. Stimulation will be automatically stopped if device detects a decrease in skin-contact area which may lead to unsafe current density to be delivered as would occur during unattended use such as sleeping.

D. Quell-FM Mobile App

Quell-FM is used with a mobile app, running on an iOS or Android mobile device, to which it communicates via Bluetooth. Using the mobile app, the user can start and stop the therapy, control stimulation intensity, and modify certain operating characteristics.

The device has a single output mode consisting of continuous stimulation at a randomly varying instantaneous frequency centered at 40 Hz (range 30 - 50 Hz), 80 Hz (default, range 60 - 100 Hz) or 160 Hz (range 120 - 200 Hz). The technical specifications are listed in **Table 1**.

Table 1. Quell-FM Output Parameters

Specification	Value
Configuration	1 stimulator (2-lead)
Waveform (e.g., pulsed monophasic, biphasic)	Biphasic with alternating leading phase, asymmetrical
Shape (e.g., rectangular, spike, rectified sinusoidal)	Rectangular
Regulated current or voltage	current
Maximum Output Voltage (+/- 5%)	50 V @ 500 Ω 118 V @ 2000 Ω 118 V @ 10000 Ω
Maximum Output Current (+/- 10%)	100 mA @ 500 Ω 61 mA @ 2000 Ω 12 mA @ 10000 Ω
Duration of primary (depolarizing) phase	100 µs
Pulse Duration	280 µs (does not include 100 µs inter-phase delay)
Pulse Frequency	60-100 Hz (default, randomly varying) 30-50 Hz (randomly varying) or 120-200 Hz (randomly varying)
Net Charge per pulse (If zero, state method of achieving zero net charge.)	Normally 8 µC @ 500 Ω per pulse; Normally 0 µC per sequential pair of pulses; zero net current
Maximum Phase Charge	18 µC @ 500 Ω 18 µC @ 1000 Ω
Maximum Current Density (r.m.s), Calculated for minimum electrode area of 28 cm^2	0.54 mA/cm^2 @ 500 Ω @80 Hz 0.76 mA/cm^2 @ 500 Ω @160 Hz
Maximum Average Current	2.2 mA @ 500 Ω @80 Hz 4.5 mA @ 500 Ω @160 Hz
Maximum Average Power Density, Calculated for minimum electrode area of 28 cm^2	4.0 mW/cm^2 @ 500 Ω @80 Hz 8/0 mW/cm^2 @ 500 Ω @160 Hz

PROCEDURE DESCRIPTION

Quell-FM delivers therapy automatically as repeating 1-hour sessions with a 1-hour gap between sessions (or 30 minutes sessions and 30 minutes gap), as long as the device is on the body, including overnight. Quell-FM provides continuous stimulation during each session. The stimulation intensity is initially set to a strong but comfortable level through the calibration procedure and can subsequently be manually adjusted by users. The intensity increases slowly during a therapy session (starting after 10 minutes) to compensate for nerve desensitization to

electrical stimulation (habituation). By default, the intensity increases 0.3% per minute in a stepwise fashion (i.e., increase by 0.3% at one-minute intervals); this is equivalent to a 16% increase over a 60-minute therapy session.

Quell-FM can be used during wakefulness or sleep. Stimulation will stop if the device detects that stimulation cannot be correctly and safely delivered, i.e., "trip condition" (**Table 2**). The user may halt stimulation at any time using the mobile application or by double tapping the device case. Alternatively, stimulation will stop after the therapy session timer (typically 60-minutes) has elapsed. The device has an optional auto-restart timer. If it is enabled then a therapy session will automatically start 1 hour (30-minute option is also available) following the end of the previous session, provided that the user did not manually halt stimulation during the previous therapy session, or a trip condition did not occur.

Table 2. Quell-FM device trip conditions

Trip Condition	Description of Triggering Criteria	Purpose
No Load	Device not connected to patient	Prevent stimulation with maximum output voltage due to open circuit.
Insufficient Charge	Charge delivered during stimulation below target	Prevent stimulation that may be sub-therapeutic.
Over Load	Charge delivered during stimulation above target	Prevent stimulation that may be exceed specification limits.
Electrode Peel	Electrode dislodging from skin	Prevent high current density due to small electrode area resulting from unrecognized electrode peeling such as during sleeping.
Low Battery	Insufficient battery charge to start (<10%) or continue (≤5%) stimulating	Prevent therapy from starting or continuing if battery charge is low and ensure that sufficient charge remains for device to operate reliably in standby mode.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

Patient contacting components include the Quell-FM device enclosure, the Quell-FM Band, and the electrodes. Per ISO 10993-1:2009 "*Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*," all three patient contacting components are considered surface devices with intact skin contact with prolonged contact (24 hours to 30 days) contact duration.

The device enclosure and Band are identical to those that are currently marketed by NeuroMetrix for the Quell device cleared under K152954. Additionally, the electrodes

are identical to the currently marketed NeuroMetrix electrodes cleared under K140586. In K152954 and K140586, the patient contacting components for the subject device 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 Quell-FM does not have a shelf-life specification. The electrodes have a shelf-life of 3 years based on accelerated and actual age testing.

There are no sterilization requirements for the Quell-FM or its accessories. The user does not sterilize the device before first or repeat uses. The electrodes are for single patient use and should be replaced if the gel does not adhere to the skin, if the gel becomes soiled, if the stimulation becomes uncomfortable, or if the electrode is torn or damaged.

Cleaning and maintenance instructions for the Quell-FM have been provided in the labeling.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The Quell-FM 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."
- IEC 60601-1:2005 Ed:3.0 +A1;C1:2014 "Medical Electrical Equipment; Part 1: General requirements for basic safety and essential performance." (Equivalent to the FDA recognized consensus standard AAMI/ANSI ES60601-1:2005/(R)2012 and C1:2009/(R)2012 and, A2:2010/(R)2012 "Medical Electrical Equipment; Part 1: General requirements for basic safety and essential performance" (IEC 60601-1:2005, MOD).
- IEC 60601-1-11:2015 Ed:2.0 "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 60601-2-10:2012 Ed:2.0 "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 Quell-FM 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 (https://www.fda.gov/media/73065/download). 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 testing was performed:

- **Wireless Coexistence Testing**

  The device hardware communicates with the mobile application through a BLE and it is intended to be used in the home environment. Wireless quality of service, wireless coexistence and communication security testing was conducted per with the FDA Guidance Document "Radio Frequency Wireless Technology in Medical Devices", issued August 14, 2013 (https://www.fda.gov/media/71975/download). Results demonstrated that the system meets specifications.

- **Lithium-Ion Battery Testing**

  The Quell-FM is powered by one rechargeable 3.7V Lithium-Ion battery (500 mAh). The safety of the Quell-FM 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 waveform, the functionality of the Quell-FM as a system, and the requirements of the output stimulation parameters. Results demonstrated that the system meets specifications.

- **Electrode Bench Testing:**

  The Quell-FM is labeled for use only with compatible NeuroMetrix electrodes that have been FDA cleared under K140586. The NeuroMetrix electrodes 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 detect a decrease in skin contact area due to electrode peeling. Results demonstrated that the electrodes passed all testing.

SUMMARY OF CLINICAL INFORMATION

a. Overview

The 119-subject clinical study was a double-blind, randomized, sham-controlled trial to evaluate the effectiveness and safety of the Quell-FM by comparing 3-months of at-home treatment with a standard Quell-FM (active) or modified Quell-FM (sham) in individuals with fibromyalgia. The primary hypothesis was that active treatment would produce greater improvements in pain, somatic symptoms, and functional impairment compared to sham treatment. A second hypothesis was that subjects with higher baseline pain sensitivity by Quantitative Sensory Testing (QST) would exhibit the largest treatment effects.

b. Subject Selection

Inclusion Criteria

- age 21 or older
- able to speak and understand English
- own a smartphone that can run the Quell mobile application
- meet American College of Rheumatology 2010 diagnostic criteria for fibromyalgia, which is defined as chronic widespread pain and somatic symptoms related to fibromyalgia for at least 3-months (Wolfe et al. 2010)
- physician diagnosis of fibromyalgia in the medical record
- average pain intensity ≥ 4 on an 11-point numerical rating scale (NRS).

Exclusion Criteria

- Diagnosis of cancer or any other malignant disease
- Acute osteomyelitis or acute bone disease
- Present or past Diagnostic and Statistical Manual of Mental Disorders (DSM-V) diagnosis of schizophrenia, delusional disorder, psychotic disorder, or dissociative disorder judged to interfere with study participation
- Pregnancy
- Any clinically unstable systemic illness judged to interfere with treatment
- A pain condition requiring urgent surgery
- An active substance use disorder, such as cocaine or IV heroin use (positive on the Mini International Neuropsychiatric Interview; M.I.N.I. v.5.0), that would interfere with study participation
- Have an implanted cardiac pacemaker, defibrillator, or other implanted electronic device

c. Randomization

Subjects were randomized to an active or sham device with equal allocation. Active and sham devices were physically identical; only differing in whether they were loaded with standard software or modified software that implemented a sham stimulation protocol. The study coordinators and investigators could not determine whether a device was an active or sham device based on markings or physical characteristics and did not discuss the stimulation experience with subjects. Subjects were told that two types of TENS were being evaluated, a "low intensity" device and a "high intensity" device. Blinding effectiveness for subjects and study coordinators was assessed at the end of the study.

d. Quantitative Sensory Testing

The Quantitative Sensory Testing (QST) procedures used to identify subjects diagnosed with fibromyalgia that had lower vs. higher pain sensitivity included mechanical and cold stimuli. Responses to punctate mechanical stimuli were measured using a standard set of weighted probes. Singular taps were performed on the metacarpophalangeal joint of the middle finger. Mechanical temporal summation was defined as the increase in pain from the first to the tenth stimulus. A pressure algometer was used to measure pain pressure thresholds (PPT) at the trapezius muscle and thumb joint. Cuff algometry at the calf was used to assess responses to sustained mechanical pressure. Responses to noxious cold were evaluated using a repeated cold pressor task, which involved immersion of the right hand in a circulating water bath maintained at 4°C. Conditioned pain modulation was measured by assessing PPT at the trapezius during the water bath immersions.

e. Intervention

The standard Quell-FM device (active) provided 60-minutes of continuous stimulation during each 1-hour therapy session. The modified Quell-FM device (sham) provided three 2-minute periods of stimulation during each session (at 0, 28, and 58 minutes) for a total of 6-minutes of stimulation. The device placement on the upper calf and usage instructions were identical for the two devices. Subjects were instructed to maintain a strong but comfortable stimulation intensity and to use their device for at least two 1-hour therapy sessions each day over the course of the study.

All subjects were asked to continue their pre-study analgesic medications with changes tracked through a weekly interview.

f. Study Endpoints:

Safety:

Adverse events were assessed in weekly phone calls with subjects.

Effectiveness:

The clinical study included one pre-specified primary effectiveness measure and seven pre-specified secondary effectiveness measures as shown in Table 3.

Table 3. Pre-specified primary and secondary effectiveness measures

Effectiveness Measures	Description

Primary	
Patient's Global Impression of Change (PGIC)	Overall belief about the effectiveness of treatment. This study included two PGIC measures per Hurst and Bolton, a 7-point categorical verbal scale (PGIC-VRS) and an 11-point numerical rating scale (PGIC-NRS). The VRS ranged from (1) "no change or condition has gotten worse" to (7) "a great deal better and a considerable improvement that has made all the difference." The use of PGIC-VRS was prespecified in the protocol and included in the statistical analyses.
Secondary	
Fibromyalgia Impact Questionnaire Revised (FIQR)	Fibromyalgia specific instrument for assessment of disease impact and health-related quality-of-life (QoL). It is comprised of 21 individual items each rated on an 11-point NRS. The FIQR Total Score ranges from 0 to 100, with higher scores indicating more fibromyalgia related impairment. FIQR is composed of three subscales: function, overall impact and symptoms. The symptom subscale includes a pain intensity assessment (FIQR pain item) that may be analyzed separately and was used in the responder analyses.
Brief Pain Inventory Short Form (BPI)	Assessment of pain severity and interference rated on an 11-point NRS. BPI Severity is the average of 4 pain intensity items. Pain Interference is the average of 7 function items. BPI Severity and BPI Interference were analyzed as distinct effectiveness measures.
painDETECT Questionnaire (PDQ)	Assessment of the presence and severity of neuropathic pain. The painDETECT questionnaire is composed of 7 pain-quality items and 2 items for pain-course and pain-radiation. Recent studies have shown that the 7-item painDETECT questionnaire has better discrimination for neuropathic pain compared to the full 9-item instrument and was therefore used in this study. The 7-item score ranges from 0 to 35, with higher scores indicating greater neuropathic pain.
Pain Disability Index (PDI)	Assessment of pain related disability. Score ranges from 0 to 70, with higher scores indicating greater pain related disability.
Hospital Anxiety and Depression Scale (HADS)	Assesses the severity of anxious and depressive symptoms. Score ranges from 0 to 42, with higher scores indicating greater severity of anxiety and depression. HADS is composed of two subscales: anxiety and depression.
Pain Catastrophizing Scale (PCS)	Assessment of pain rumination, magnification, and helplessness. Score ranges from 0 to 52, with higher scores indicating greater catastrophic thinking.

g. Statistical Analysis

The primary analysis of treatment effects was conducted in the intention-to-treat (ITT) population, which included all 119 randomized subjects.

One pre-specified subgroup analysis was carried out in the ITT population. The study protocol predicted that subjects with higher pain sensitivity based on QST measures would demonstrate the greatest treatment effects. Subjects were classified as having lower or higher pain sensitivity by their baseline QST data. Principal component analysis was applied to the correlation matrix of the baseline QST data to identify the prominent pain patterns in the study population. The first principal component accounted for 40% of the total variance. The component had negative loadings for mechanical pain thresholds, positive loadings for pain responses to punctate stimuli and cold stimuli, and a positive loading for temporal summation, and could therefore be interpreted as a composite index of pain sensitivity. Subjects were classified as lower (< median) or higher (≥ median) pain sensitivity using this principal component. This yielded a lower pain sensitivity subgroup with 59 subjects and a higher pain sensitivity subgroup with 60 subjects.

The 3-month least-squares (LS) mean PGIC scores were compared between the active and sham treatment groups, controlling for baseline pain severity (BPI average pain item), tenderness (dichotomized FIQR tenderness item) and body mass index (BMI) with an ANCOVA model. Missing scores were filled in using single imputation. Significance was assessed by the two-sample t-test with a Type I error rate of 0.05 (two-sided). The subgroup analysis was conducted to test for heterogeneity in the treatment response based on pain sensitivity. Between and within subgroup treatment effects were assessed with the primary ANCOVA model that included a treatment by subgroup interaction.

The baseline to 3-month LS mean change scores for the secondary effectiveness measures were compared between the active and sham treatment groups, controlling for baseline value, pain severity, tenderness and BMI with an ANCOVA model. Missing data were filled in using multiple imputation. Significance was assessed by the two-sample t-test with a Type I error rate of 0.05 (two-sided).

Responder analyses for PGIC, FIQR Total Score and pain intensity (FIQR pain item) were conducted to inform the clinical meaningfulness of treatment effects. Responder rates were compared between treatment groups using logistic regression, controlling for baseline pain severity, tenderness and BMI. P-values were not assessed against a significance threshold because the study was not specifically powered for responder analyses.

h. Results

Of the 170 individuals screened for the study, 119 met the inclusion/exclusion criteria and were randomized to an active (62) or a sham (57) device for 3-months. Among these subjects, 19 (10 active, 9 sham) withdrew; 16 (7 active, 9 sham) were lost to follow-up and 3 (3 active, 0 sham) withdrew but completed the 3-month assessments. The remaining 100 subjects completed 3-months of treatment, however 4 (1 active, 3 sham) did not return the 3-month assessments via mail following implementation of COVID-19 restrictions on in-person clinic visits.

Analgesic Use

At the baseline, half of the subjects ([b)(4)]%) were taking over-the-counter analgesics, [b)(4)]% were prescribed neuroleptics, [b)(4)]% were prescribed an antidepressant and [b)(4)]% were taking an opioid, including tramadol. At the baseline, [b)(4)]% and [b)(4)]% of the participants in the sham and active treatment groups use pain medication. There was no discernable change

in analgesic use over the course of the study and there were no significant differences between the treatment groups for any week.

Device Use

Table 4 displays key characteristics of the distributions for Therapy Hours and Wear Time (Hours) for subjects randomized to receive the active device or sham device. One therapy hour (also called therapy session) equals 1 hour of electrical stimulation. Wear Time represents the total amount of time the device is on the patient's skin and is approximated as (2x Therapy Hours – 1 hour) rounded down to the nearest hour.

Table 4. Distribution of daily therapy hours for subjects randomized to the active device or sham device

	Sham Arm (n=59)	Active Arm (n=60)	All Subjects (N=119)
Therapy Hours*			
Median	3.9	3.8	3.8
75th Percentile	5.4	5.8	5.6
95th Percentile	8.4	8.4	8.4
Wear Time (Hours)†			
Median	6	6	6
75th Percentile	9	10	10
95th Percentile	15	15	15

*One therapy hour (also called therapy session) represents 1-hour of electrical stimulation.

†Wear time represents the total amount of time the device is on the patient's skin and is approximated as (2 x Therapy Hours - 1 hour) rounded down to the nearest hour.

Blinding Assessment

Blinding was assessed as each subject completed the study by asking the coordinators and subjects to identify whether a low intensity or high intensity Quell-FM device was used. The coordinator identified the correct treatment in 54.7% (95% CI [45.2, 64.2]) of the 103 subjects that completed the study (n=100) or withdrew but provided the 3-month assessment (n=3). The treatment was correctly identified 63.8% (95% CI [51.4, 76.2]) of the time for the active device and 43.8% (95% CI [29.7%, 57.8%]) of the time for the sham device.

Of the 99 subjects that completed the 3-month assessment, 86 answered the blinding question which was included in the satisfaction questionnaire. Among the 13 that did not answer this question, 3 did not complete any part of the satisfaction questionnaire. In the subjects that answered the blinding question, 50.0% (95% CI [39.4, 60.6]) identified the correct treatment. Subjects in the active group correctly identified their treatment 17.4% (95% CI [6.4, 28.3]) of the time and subjects in the sham group correctly identified their treatment 87.5% (95% CI

[77.3, 97.7]) of the time. Among all subjects, 84.9% (95% CI [77.3, 92.5]) believed they received a low intensity device.

Safety Endpoint

A total of 12 (5 active, 7 sham) adverse events were reported. They included rash at the site of the device, numbness and tingling, and muscle cramping. Six (3 active, 3 sham) were determined to be related to TENS use, 3 (1 active, 2 sham) were deemed possibly related to TENS use, and 3 (1 active, 2 sham) were judged to be unrelated to TENS use by the principal investigator. The 9 events that were definitely or possibly related to TENS use were minor and self-limited. The most common occurrence was a rash under the Quell- FM electrodes. Ten subjects averaged more than 8 therapy hours (i.e., about 15 wear hours) per day (**Table 4**). Among these ten subjects, one experienced skin irritation that resolved after 1-week of not wearing their device. These ten subjects did not report any other adverse events. Skin irritation is a known minor risk of TENS use that generally resolves with conservative measures.

Primary Effectiveness Outcome

The difference in the LS mean PGIC scores between active (3.54, SE 0.25) and sham (3.14, SE 0.26) treatment at 3-months was not significant in the ITT population (mean difference 0.40, 95% CI [-0.33, 1.13], p=0.279) (**Figure 2**). In the pre-specified subgroup analysis, the interaction between treatment and baseline pain sensitivity was significant (p=0.020), which indicated that baseline pain sensitivity moderated the relationship between treatment and PGIC at 3-months. In the higher pain sensitivity subgroup, PGIC was significantly greater for active treatment compared to sham treatment (mean difference 1.25, 95% CI [0.25, 2.24], p=0.015). The difference between active treatment and sham treatment in subjects with lower pain sensitivity was not significant (mean difference -0.45, 95% CI [-1.48, 0.58], p=0.393).

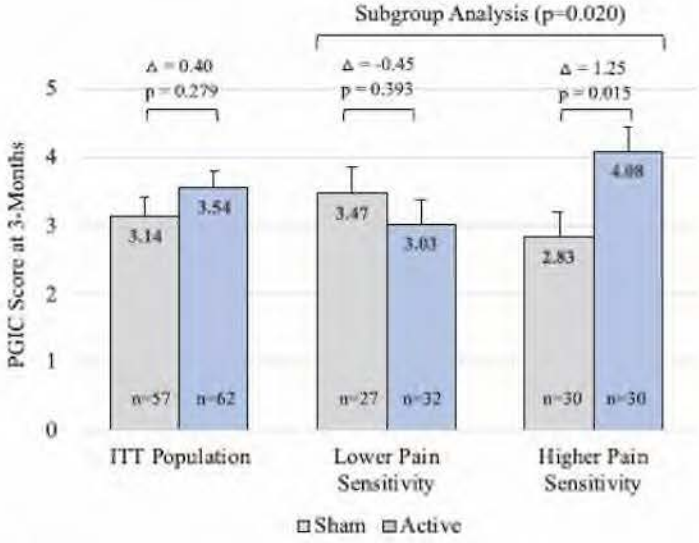

Figure 1. Comparison of PGIC in ITT population and in pain sensitivity subgroups

Secondary Effectiveness Endpoints

Table 5 shows the 3-month LS mean change scores for the pre-specified secondary effectiveness measures in the ITT population. Negative values indicate improvement. All seven effectiveness measures showed significant within-group (i.e., baseline to 3-months) improvements for active treatment compared to 4 of 7 for sham treatment. The within-group improvements for active treatment were numerically greater than sham treatment for all measures except PCS. The treatment group differences were significant in the FIQR Total Score (-8.58, 95% CI [-15.44, -1.72], p=0.015), BPI Interference (-0.86, 95% CI [-1.64, -0.08], p=0.031), PDQ (-2.21, 95% CI [-3.90, -0.15], p=0.027) and PDI (-4.90, 95% CI [-9.65, -0.14], p=0.044).

Table 5. LS mean changes in secondary effectiveness measures from baseline to 3-months for the ITT population.

					Treatment Comparison (Active - Sham)		
Measure	**N**	**Mean**	**SE**		**Diff**	**95% CI**	**p-value**
FIQR Total Score							
Sham	57	-5.07†	2.53				
Active	62	-13.65‡	2.23		-8.58	-15.44, -1.72	0.015
FIQR Pain Item*							
Sham	57	-1.01‡	0.26				
Active	62	-1.72‡	0.24		-0.71	-1.44, 0.02	0.055
BPI Severity							
Sham	57	-0.80†	0.23				
Active	62	-1.28‡	0.22		-0.48	-1.13, 0.17	0.144
BPI Interference							
Sham	57	-0.95†	0.28				
Active	62	-1.81‡	0.26		-0.86	-1.64, -0.08	0.031
PDQ							
Sham	57	0.13	0.71				
Active	62	-2.08†	0.65		-2.21	-3.90, -0.15	0.027
PDI							
Sham	57	-2.40	1.76				
Active	62	-7.30‡	1.54		-4.90	-9.65, -0.14	0.044
HADS							
Sham	57	-0.88	0.71				
Active	62	-2.42‡	0.66		-1.54	-3.52, 0.43	0.124
PCS							
Sham	57	-4.37†	1.25				
Active	62	-3.66†	1.16		0.70	-2.73, 4.14	0.684

Notes: Missing data imputed by MICE. Negative values indicate improvement. *FIQR Pain Item is a component of FIQR Total Score and is separately listed for informational purposes. †Significant within group improvement by one-sample t-test, p<0.05. ‡Significant within group improvement by one-sample t-test, p<0.001. p-value, two-sample t-test.

Table 6 shows the 3-month LS mean change scores for the secondary effectiveness measures in the subgroup with high pain sensitivity. Negative values indicate improvement. Six of 7 effectiveness measures showed significant within-group (i.e., baseline to 3-months) improvements for active treatment compared to 1 of 7 for sham treatment. The within-group improvements for active treatment were numerically greater than sham treatment for all measures. The treatment group differences were significant for FIQR Total Score ((b)(4) 95% CI (b)(4) p=0.031), FIQR Pain Item ((b)(4) 95% CI (b)(4) p=0.003),

BPI Severity ([redacted] 95% CI [redacted], p=0.035) and PDQ [redacted] 95% CI [redacted] p=0.018).

Table 6. LS mean changes in secondary effectiveness measures from baseline to 3-months in the subgroup with high pain sensitivity

				Treatment Comparison (Active - Sham)		
Measure	**N**	**Mean**	**SE**	**Diff**	**95% CI**	**p-value**
FIQR Total Score						
Sham	30	-2.66	3.96			
Active	30	-13.97‡	3.24	-11.31	-21.55, -1.07	0.031
FIQR Pain Item*						
Sham	30	-0.69	0.38			
Active	30	-2.25‡	0.36	-1.57	-2.59, -0.54	0.003
BPI Severity						
Sham	30	-0.31	0.34			
Active	30	-1.30‡	0.31	-0.99	-1.90, -0.07	0.035
BPI Interference						
Sham	30	-0.78	0.40			
Active	30	-1.86‡	0.37	-1.09	-2.18, 0.00	0.051
PDQ						
Sham	30	0.68	1.00			
Active	30	-2.68†	0.95	-3.35	-6.13, -0.58	0.018
PDI						
Sham	30	-0.99	2.62			
Active	30	-7.35†	2.26	-6.37	-13.16, 0.43	0.066
HADS						
Sham	30	-0.90	1.01			
Active	30	-1.90	0.97	-0.99	-3.74, 1.75	0.474
PCS						
Sham	30	-3.78†	1.76			

Table 7 shows 3-month LS mean change scores of the 21 items comprising the FIQR Total Score in the ITT population. FIQR is a comprehensive health related Quality of Life (QoL) assessment specifically designed for fibromyalgia. It captures pain, somatic symptoms, activities of daily living and overall disease impact. The purpose of this post-hoc analysis is to determine if active treatment broadly improves fibromyalgia symptoms or disproportionally impacts certain symptoms. For active treatment, 19 of 21 symptoms exhibited a significant improvement from baseline to 3-months compared to 5 of 21 for sham treatment. Similarly, 16 of 21 symptoms decreased by at least 1 point compared to 2 of 21 for sham treatment. The active group exhibited significantly better improvement than sham for 9 of the 21 symptoms.

Table 7. LS mean changes in symptoms of fibromyalgia from baseline to 3-months in the ITT population

			Treatment Comparison (Active - Sham)	
FIQR Item (11-point NRS)	Sham	Active	Difference	p-value
Pain	-1.01 (0.26)‡	-1.72 (0.24)‡	-0.71 (0.36)	0.055

Sleep	-0.55 (0.42)	-1.56 (0.37)‡	-1.01 (0.58)	0.086
Fatigue	-0.06 (0.35)	-1.23 (0.31)‡	-1.17 (0.48)	0.016
Sensitivity	-1.12 (0.41)†	-1.06 (0.38)†	0.06 (0.57)	0.917
Tenderness	-0.21 (0.36)	-0.64 (0.30)†	-0.43 (0.48)	0.373
Stiffness	-0.60 (0.32)	-1.24 (0.29)‡	-0.64 (0.44)	0.150
Balance	-0.35 (0.34)	-1.32 (0.30)‡	-0.97 (0.46)	0.039
Anxiety	-0.56 (0.37)	-0.41 (0.31)	0.14 (0.49)	0.771
Depression	-0.16 (0.37)	-0.69 (0.31)†	-0.53 (0.50)	0.294
Memory	-0.71 (0.36)†	-0.85 (0.31)†	-0.13 (0.48)	0.785
Goals disrupted by fibromyalgia	-0.72 (0.40)	-1.89 (0.33)‡	-1.16 (0.53)	0.031
Overwhelmed by symptoms	-0.86 (0.39)†	-2.23 (0.34)‡	-1.37 (0.52)	0.010
Ability to walk	-0.76 (0.37)†	-1.22 (0.35)†	-0.46 (0.52)	0.379
Ability to climb stairs	-0.08 (0.35)	-1.05 (0.33)†	-0.98 (0.49)	0.050
Ability to clean floors	-0.37 (0.43)	-1.32 (0.39)†	-0.96 (0.59)	0.108
Ability to shop for groceries	-0.11 (0.38)	-1.15 (0.34)†	-1.05 (0.52)	0.049
Ability to prepare meal	-0.42 (0.36)	-1.29 (0.31)‡	-0.87 (0.48)	0.072
Ability to comb hair	-0.21 (0.31)	-0.51 (0.29)	-0.30 (0.43)	0.484
Ability to change bed sheets	-0.23 (0.37)	-1.37 (0.32)‡	-1.14 (0.50)	0.025
Ability to carry bag of groceries	-0.31 (0.37)	-1.43 (0.33)‡	-1.12 (0.50)	0.029
Ability to sit for 45 minutes	-0.31 (0.39)	-1.62 (0.36)‡	-1.31 (0.54)	0.016

Notes: Missing data imputed by MICE (250 data sets imputed for each item). Negative values indicate improvement. †Significant within group improvement by one-sample t-test, $p<0.05$. ‡Significant within group improvement by one-sample t-test, $p<0.001$. p-value, two-sample t-test.

Responder Analyses

A PGIC responder was defined as a subject with a score ≥ 5 at 3-months, which corresponds to moderately better symptoms, functional abilities and overall health. Forty-three percent (43%) of active treatment subjects in the ITT population and 58% in the higher pain sensitivity subgroup were PGIC responders (Table 8). The difference in the responder rate between active and sham treatment was 28% ($p=0.025$) in the higher pain sensitivity subgroup.

Table 8. PGIC responder analysis.

Population	Sham % (SE)	Active % (SE)	Diff (95% CI)	p-value
ITT (N=119)	34.6 (6.3)	42.4 (6.3)	7.8 (-9.9, 25.5)	0.389
Subgroup Analysis (N=119)				
Higher Pain Sensitivity (n=60)	30.2 (8.4)	57.8 (9.2)	27.7 (3.5, 51.8)	0.025
Lower Pain Sensitivity (n=59)	39.1 (9.7)	28.2 (8.0)	-10.9 (-35.5, 13.7)	0.385

Notes: Responder defined as score ≥ 5 at 3-months.

Abbreviations: SE, standard error. CI, confidence interval. ITT, intention to treat.

A FIQR responder was defined as a subject that exhibited ≥ 15% reduction in their FIQR Total Score from baseline to 3-months. This threshold corresponds to the minimal clinically important difference. Fifty-seven percent (57%) of active treatment subjects in the ITT population and 58% in the higher pain sensitivity subgroup were FIQR responders (Table 9). The difference in the responder rate between active and sham treatment was 23% in the ITT population (p=0.014) and 30% (p=0.019) in the higher pain sensitivity subgroup.

Table 9. FIQR Total Score responder analysis.

Population	Sham % (SE)	Active % (SE)	Diff (95% CI)	p-value
ITT (N=119)	34.0 (6.4)	56.9 (6.5)	22.9 (4.7, 41.0)	0.014
Subgroup Analysis (N=119)				
Higher Pain Sensitivity (n=60	28.1 (8.7)	57.5 (9.2)	29.5 (4.8, 54.1)	0.019
Lower Pain Sensitivity (n=59)	40.3 (9.7)	55.8 (9.0)	15.5 (-10.4, 41.5)	0.240
Notes: Responder defined as ≥ 15% reduction from baseline to 3-months. Abbreviations: SE, standard error. CI, confidence interval. ITT, intention to treat.				

A pain intensity responder was defined as a subject that exhibited a ≥ 30% or ≥ 50% reduction in their pain rating (FIQR pain item) from baseline to 3-months. The 30% cutoff represents moderate improvement in pain and the ≥ 50% cutoff represents a substantial improvement in pain. **Table 10** shows the pain intensity responder rates. Forty-six percent (46%) of active treatment subjects in the ITT population and 60% in the higher pain sensitivity subgroup were responders at the ≥ 30% level or moderate improvement. Substantial improvement (≥ 50% reduction) was exhibited by 27% of subjects in the ITT population and 43% in the higher pain sensitivity subgroup. The moderate improvement responder rate was 17% greater for active treatment compared to sham (p=0.074). In the higher pain sensitivity subgroup, active treatment was greater than sham by 42% (p=0.001). A similar pattern was observed for substantial improvement responder rates.

Table 10. Pain intensity responder analysis.

Population	Sham % (SE)	Active % (SE)	Diff (95% CI)	p-value
≥ 30% Reduction in pain intensity from baseline to 3-months (moderate improvement)				
ITT (N=119)	29.3 (6.2)	45.8 (6.7)	16.5 (-1.6, 34.6)	0.074
Subgroup Analysis (N=119)				
Higher Pain Sensitivity (n=60)	17.5 (7.6)	59.5 (9.6)	41.9 (18.6, 65.3)	<0.001
Lower Pain Sensitivity (n=59)	40.3 (10.0)	33.1 (8.6)	-7.3 (-33.1, 18.6)	0.582

≥ 50% Reduction in pain intensity from baseline to 3-months (substantial improvement)				
ITT (N=119)	12.5 (4.4)	27.3 (6.0)	14.8 (0.03, 29.4)	0.045
Subgroup Analysis (N=119)				
Higher Pain Sensitivity (n=60)	8.7 (5.6)	43.1 (9.8)	34.4 (12.8, 56.1)	0.002
Lower Pain Sensitivity (n=59)	15.3 (6.7)	14.9 (6.5)	-0.4 (-18.7, 17.9)	0.967

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 Prescription devices.

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 Quell-FM device. It 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 11 below identifies the risks to health that may be associated with use of the transcutaneous electrical nerve stimulator to treat fibromyalgia symptoms and the measures necessary to mitigate these risks.

Table 11. Identified Risks to Health and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Adverse tissue reaction	Biocompatibility evaluation
Skin discomfort, burns, electrical shock, or pain at stimulation site	Electromagnetic compatibility testing Electrical, mechanical, and thermal safety testing Non-clinical performance testing Software verification, validation, and hazard analysis Labeling
Device failure due to interference with other devices	Electromagnetic compatibility (EMC) testing Software verification, validation, and hazard analysis

	Labeling
Delayed or ineffective treatment due to user error	Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the transcutaneous electrical nerve stimulator to treat fibromyalgia symptoms 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:
    a) 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);
    b) Characterization of the impedance monitoring system; and
    c) Characterization of electrode performance, including the electrical performance, adhesive integrity, shelf life, reusability, and current distribution of the electrode surface area.
2. The patient-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. Labeling must include the following:
    a) Recommended treatment regimes, including but not limited to, frequency and duration of use, application site(s), and typical sensations experienced during treatment;
    b) A shelf life for the electrode and reuse information;
    c) Summaries of the electrical stimulation parameters and device technical parameters (including any wireless specifications); and
    d) Instructions on how to correctly use and maintain the device, including all user-interface components.

BENEFIT/RISK DETERMINATION

The risks of the Quell-FM device were established with data collected in nonclinical studies (e.g., biocompatibility, electrical safety, EMC, and software testing) as well as data collected in the clinical trial described above and are generally well understood. Specifically,

a. The results of the nonclinical testing demonstrated that the Quell-FM performed as per specifications and the results did not raise concerns regarding risks to the patients.

b. There were no serious adverse events reported in the study. Nine adverse events reported in the clinical trial were judged to be definitely or possibly related to the use of Quell-FM, all of which were minor and self-limited. The most common adverse event experienced when using the Quell-FM device to treat the symptoms of fibromyalgia was a mild rash at the site of electrode placement, a known side-effect of TENS devices that typically resolves quickly with conservative measures. Should any adverse reactions or discomfort occur, the user can reduce or halt the stimulation at any time using the mobile application or double tapping the device.

c. The provided IFU and labeling (i.e., description of clinical study results) will guide physicians towards prescribing Quell-FM to treat the patient population demonstrated to be most responsive to the therapy.

d. Any patient diagnosed with fibromyalgia that does not experience improvement with the Quell-FM can stop treatment without negative physiological effects (e.g., withdrawal symptoms).

The probable benefits of the device are based on data collected in the clinical study. Although many participants in the clinical study were also taking medication for fibromyalgia and it was difficult to assess the effects of the device compared to medication, there are several clinically meaningful benefits for using the Quell-FM as an aid for reducing the symptoms of fibromyalgia in adults, especially in those with high pain sensitivity. Specifically,

a. Primary endpoint: Although the trial did not meet its primary effectiveness endpoint of a significant treatment group difference in the 3-month mean PGIC scores, it is important to note that the difference of 0.4 points in the ITT analysis was similar to that observed in trials of FDA approved drugs widely used for management of fibromyalgia. Therefore, Quell-FM treatment of fibromyalgia patients exhibited comparable benefits when compared to FDA-approved drug therapies for fibromyalgia, with none of the side effects that are intolerable for some patients such as nausea, dizziness, and somnolence. Moreover, in subjects with higher baseline pain sensitivity, the mean PGIC score for those receiving active treatment was 1.2-points greater than those receiving sham treatment. This difference was statistically significant ($p=0.015$) and clinically meaningful. These results are also consistent with the pain intensity responder analysis, which demonstrated a larger group difference in responder rates in the higher pain sensitivity subgroup compared to the entire ITT population.

b. Secondary endpoints: The active treatment was favored in the following secondary endpoints.

    i. Statistically and clinically meaningful improvement in health-related quality of life compared to sham as measured by the FIQR instrument.

    ii. Improvement in multiple effectiveness measures over three months that include pain severity (including neuropathic symptoms), pain interference with function, pain related disability and psychological impairment. The improvement in neuropathic symptoms (PDQ), pain interference with function (BPI-SF Interference), and pain related disability (PDI) were significant compared to sham.

    iii. Pressure pain threshold at the trapezius was significantly increased compared to sham,

indicating a reduction in hyperalgesia.

Thus, Quell-FM provides clinically meaningful relief from fibromyalgia symptoms.

Patient Perspectives

Patient perspectives considered for the Quell-FM included patient reported outcomes (PROs) that assess patients' impression about the treatment effectiveness and disease impact, including the primary effectiveness outcome PGIC, secondary effectiveness outcome FIQR, and pain outcomes.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for the Quell-FM device for the following indications for use statement:

> The Quell-FM is a transcutaneous electrical nerve stimulation (TENS) device indicated as an aid for reducing the symptoms of fibromyalgia in adults with high pain sensitivity. The Quell-FM may be used during sleep. The Quell-FM is labeled for use only with compatible NeuroMetrix electrodes.

The Quell-FM 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 Quell-FM is granted and the device is classified under the following:

Product Code: QSQ
Device Type: Transcutaneous electrical nerve stimulator to treat fibromyalgia symptoms
Class: II
Regulation: 21 CFR 882.5888

REFERENCE

Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)*. May 2010;62(5):600-10.