# DE NOVO CLASSIFICATION REQUEST FOR CLEARUP SINUS RELIEF

## REGULATORY INFORMATION

FDA identifies this generic type of device as:

**Transcutaneous electrical nerve stimulator for the relief of congestion.** A transcutaneous electrical nerve stimulator for the relief of congestion is a device that electrically stimulates the skin overlying the paranasal sinuses to relieve congestion.

**NEW REGULATION NUMBER:** 21 CFR 874.6000

**CLASSIFICATION:** Class II

**PRODUCT CODE:** QNU

## BACKGROUND

**DEVICE NAME:** ClearUP Sinus Relief

**SUBMISSION NUMBER:** DEN200006

**DATE OF DE NOVO:** February 13, 2020

**SPONSOR INFORMATION:**

Tivic Health Systems Inc.
750 Menlo Ave # 200
Menlo Park, CA 94025

## INDICATIONS FOR USE

ClearUP Sinus Relief device is a transcutaneous electrical nerve stimulator that electrically stimulates the skin overlying the paranasal sinuses and is intended to be used for the temporary relief of moderate to severe congestion. ClearUP Sinus Relief is a treatment to be used at home by individuals 18 and older.

### LIMITATIONS

WARNINGS

- Do not use if you have implanted electrostimulation devices including a pacemaker, a DBS (Deep Brain Stimulation) device, hearing or visual implant devices (e.g., cochlear implant, auditory brainstem implant, retinal prostheses).
- Do not use if you have active implanted metallic devices in the treatment path (i.e., cheek, nose and brow bone).

- Do not use if you currently have abnormal cranial nerve or other neurological findings or symptoms that would require prompt medical attention.
- Do not use if the device enclosure or tip is damaged.
- Do not use device if the Treatment Intensity Level light is continually flashing. This indicates a device fault. Contact Customer Service.
- Do not use if metal components are hot to the touch.
- Do not alter the device.
- Stop device use and consult your physician if you experience any discomfort, increased pain, or any adverse reaction.
- If you have had medical or physical treatment for your pain, consult with your physician before using this device.
- If you have suspected or diagnosed heart disease, you should follow precautions recommended by your physician.
- Do not apply stimulation in the presence of electronic monitoring equipment (e.g., cardiac monitors, ECG alarms) because it may disrupt the proper operation of the equipment.
- Immediately remove the probe tip from face if you feel discomfort or muscle twitching of the eye.

CAUTIONS

- Discontinue using the device if you are not experiencing symptom reduction after two weeks of use.
- Do not use if the skin is broken or on a wound of any kind.
- Do not insert device into the nose or inside any other body part.
- Do not put the device directly on or in your eyes or ears, on your neck, or on any body part not indicated.
- Wipe off the tip of device with alcohol or water before each use. Do not immerse in any fluid.
- Do not share the device with other users.
- Do not use if wearing facial piercings or metal jewelry.
- Do not use in a bathtub, shower, or steam room.
- Do not use in a moving vehicle.
- Do not use device while charging since device is disabled during charging.
- Do not use if you experience any unusual skin sensitivity such as exaggerated writing on the skin when the skin is stroked.
- Keep out of reach of children and store it safely away from children.

- Portable RF communications equipment (including peripherals such as antenna cables and external antennas, security systems, cell phones) should be used no closer than 30 cm (12 inches) to any part of the ClearUP device including cables specified by the manufacturer. Otherwise, degradation of the performance of this equipment could result.
- Do not use device if it shuts down or the performance has degraded in any way.
- Do not use device near active high frequency (HF) surgical equipment or in the radio frequency (RF) shielded room of a Magnetic Resonance Imaging (MRI) scanner or near RF emitting equipment such as diathermy and electrocautery & Radio Frequency Identification (RFID) because it could result in improper operation.
- Use of the device adjacent to or stacked with other equipment should be avoided because it could result in improper operation. If such use is necessary, the device and the other equipment should be observed to verify that they are operating normally.
- Use of cables other than those specified or provided by the manufacturer of the device could result in increased electromagnetic emissions or decreased electromagnetic immunity of the device and result in improper operation.
- The safety of electrical nerve stimulation during pregnancy or delivery has not been established.

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

## DEVICE DESCRIPTION

ClearUP Sinus Relief is an over-the-counter, handheld microcurrent stimulation reusable device to be used at home by individuals 18 and older with moderate to severe congestion (Figure 1). Note that Tivic Health Systems Inc. received a 510(k) clearance (K182025) for a similar device, ClearUp Sinus Pain Relief, for the temporary relief of sinus pain associated with Allergic Rhinitis. In the current De Novo, Tivic Health Systems made minor design changes to the device, intended to be used for the temporary relief of moderate to severe congestion. The unit applies microcurrent waves at a very low level of electrical current to the skin overlying the paranasal sinuses and continuously measures skin impedance as the user glides the electrode along the skin. When the skin impedance measurement drops below a threshold, ClearUP Sinus Relief identifies this as a treatment point in the skin overlying the paranasal sinuses which allows current to pass most easily across the skin. The device indicates a treatment point with a brief haptic vibration. These low-impedance points correlate with subcutaneous nerve fibers and foramina (holes) through which major nerve fibers pass from the sinus passages, through the skull, to areas near the skin (Figure 2).

The pear-shaped device is held in the hand, with the rounded tip of the device applied to the facial skin in the region of the paranasal sinuses. The tip is the active electrode of a monopolar design. The housing of the device serves as the return electrode. The hand holding the device completes the electrical path.

Once the haptic vibration ends, the user is instructed to glide the device along the indicated path until reaching the next low-impedance area, at which point the haptic vibration will activate

again. A single treatment is 5 minutes in duration. The user may adjust the current setting of the device (low, medium, high) if they prefer more or less current intensity. The default setting for the device is low.

The device is reusable for a single user, provided non-sterile, and it is not required to be sterilized prior to use.


***Figure 1 ClearUP Sinus Relief***

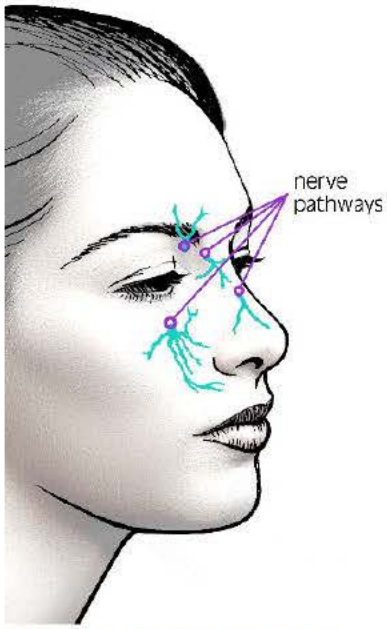


***Figure 2 Treatment Regions***

Table 1 shows the device parameters and outputs for ClearUP Sinus Relief.

***Table 1 Device parameters and outputs***

| Parameter | Output |
|---|---|
| Channel | One |
| Waveform | Biphasic with low dutycycle |
| Shape | AC-coupled square |
| Stimulation peak voltage and current | ±3V/6mA at 500Ω<br>±10V/5mA at 2kΩ<br>±20V/2mA at 10kΩ |
| Pulse duration | 250 µsec |
| Frequency | 15Hz |
| Max Current Density at 500 ohms (at tip) | 3.2mA / $cm^2$ |
| Maximum phase charge | 1.5 µC at 500Ω |

## SUMMARY OF NONCLINICAL/BENCH TESTING

The non-clinical/bench studies conducted on the ClearUP Sinus Relief are summarized in the sections below. Note that certain nonclinical/bench tests were conducted in K182025, including biocompatibility, usability study, usability engineering, software classification, and nerve and muscle stimulator test. Due to the minor design changes, Tivic Health Systems Inc. performed a new design verification, electromagnetic compatibility, and electrical safety tests for ClearUP Sinus Relief.

### BIOCOMPATIBILITY / MATERIALS

All skin-contacting ClearUP Sinus Relief device materials were tested for cytotoxicity, sensitization, and irritation per *FDA's Guidance for Industry and FDA Staff; Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process."* The results of the biological tests demonstrated that the patient contacting materials of the ClearUP Sinus Relief were found to be biocompatible, as listed in Table 2.

***Table 2 Biocompatibility Testing***

| Test Name | Test Method | Result |
|---|---|---|
| Cytotoxicity | MEM Elution ISO 10993-5:2009 | Passed |
| Sensitization | Risk evaluation assessment per ISO10993-5:2009 showed that the likelihood of adverse sensitization effect from the device is considered low. | Passed |
| Irritation | Risk evaluation assessment per 10993-5:2009 showed that the likelihood of adverse irritation effect from device is considered low. | Passed |

### PACKAGING VALIDATION

The packaging validation of the ClearUP Sinus Relief was conducted in accordance with ASTM D4332 and ASTM D4169. The packaged devices were subjected to climatic conditioning per ASTM D4332, and transit simulation per ASTM D4169, Distribution Cycle 13. These conditions challenged the ability of the packaging to protect the devices through acute storage, handling, and transit from the point of packaging to delivery to the end user. The devices showed no signs of damage and were verified to be functional after being subjected to both the climate conditioning and Simulated Transit testing. The packaging system protected the device without compromising the function and performance of the device.

### RELIABILITY TESTING

The ClearUP Sinus Relief is a durable reusable device whose lifetime will be determined by customer usage. The functionality of the ClearUP Sinus Relief was verified via software self-test each time the device is powered on. The testing showed that ClearUP Sinus Relief has a minimum product life of three (3) years based on reliability testing in its intended use environment.

### DESIGN VERIFICATION

Device design verification testing (hardware and software) was performed. The results of the testing verified the proper device output, performance, and functional characteristics of the ClearUP Sinus Relief.

### USABILITY STUDY

Human Factors and Usability Engineering study of the ClearUP Sinus Relief was performed per *FDA's Guidance for Industry and FDA Staff; Applying Human Factors and Usability Engineering to Medical Device*." The study involved (b) (4) representative users who self-reported experiencing sinus-related symptoms. The study evaluated the participants' ability to learn how to use the device correctly and safely, their understanding of the safety risks, and their subjective reactions. Overall, the study participants found that the ClearUP Sinus Relief device was easy to use, the Quick Start Guide was successful in conveying proper use, and the User's Guide provided useful information in identifying safety risks. All concerns and suggestions have been addressed in the current design of the device and/or the labeling.

### USABILITY ENGINEERING

Usability Engineering testing per IEC *62366 (2015), Medical devices application of usability engineering to medical devices,* was performed. The ClearUP Sinus Relief passed the applicable IEC 62366 testing requirements for medical equipment.

### ELECTROMAGNETIC COMPATIBILITY

The ClearUP Sinus Relief was tested for basic safety and essential performance with regard to electromagnetic disturbances and for electromagnetic emissions per IEC 60601-1-2 (2014) requirements. The ClearUP device passed IEC 60601-1-2 testing requirements for medical equipment.

### ELECTRICAL SAFETY

The ClearUP Sinus Relief was tested for basic safety and essential performance per IEC 60601-1 (2005/(R) 2012 and A1:2012), IEC 60601-1-6 (2010) and IEC 60601-1-11 (2015). The ClearUP Sinus Relief passed IEC 60601-1, IEC 60601-1-6, and IEC 60601-1-11 testing requirements for medical equipment.

### SOFTWARE

A failure or latent flaw in the software for the ClearUP Sinus Relief device could indirectly result in patient injury; therefore, the software of this device is considered to have a "Moderate" level of concern. All the elements of software documentation were fulfilled corresponding to the "Moderate" level of concern, as outlined in the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices." Adequate documentation describing the software/firmware, software specifications, architecture design, software development environment, traceability, revision level history, unresolved anomalies provide the foundation that the software operates in a manner as described in the specifications. Hazard analysis was performed to characterize software risks including device malfunction and measurement related errors. Verification and validation (V&V) testing was performed to address the potential hazards with satisfactory results.

### NERVE AND MUSCLE STIMULATOR

The ClearUP Sinus Relief was tested for basic safety and essential performance of nerve and muscle simulators per IEC 60601-2-10 (2016) requirements. The ClearUP Sinus Relief passed IEC 60601-2-10 testing requirements for medical equipment.

### BATTERY SAFETY

The ClearUP Sinus Relief uses an off-the-shelf rechargeable lithium battery, which conforms to IEC 62133-2 (basic safety requirements for portable sealed secondary cells, and for batteries made from them, for use in portable applications – Lithium systems) requirements.

## SUMMARY OF CLINICAL INFORMATION

### CONGESTION STUDY 1 - A USER STUDY OF CLEARUP SINUS RELIEF

#### STUDY OBJECTIVE

The primary endpoint of the study was to demonstrate that the average decrease in pain score for subjects treated with the active ClearUP Sinus Relief device is greater than the average decrease in pain score for subjects treated with the sham/placebo device. In addition to the pain outcome, the study also demonstrated that the average decrease in congestion for the subjects treated with the active ClearUP Sinus Relief device was greater than the average decrease in congestion for the subjects treated with the sham/placebo device. Congestion measurements were obtained using the Nasal Obstruction Symptom Evaluation (NOSE) questionnaire (Stewart et al., 2004), a validated and widely used self-report instrument for quantifying congestion[1]. For the current study, the NOSE questionnaire was modified to remove Questions 4 and 5 as they are related to the impact of congestion on sleep and exertion and are not relevant in the context of an outpatient visit assessing the acute effects of ClearUP Sinus Relief device. Questions 1-3 in the NOSE questionnaire were not changed and the Modified NOSE questionnaire maintained the psychometric validity in the quantification of congestion symptoms.

#### STUDY DESIGN

This study was a double blinded randomized sham-controlled trial. A total 71 subjects suffering from sinus pain were recruited from a tertiary rhinology practice and from the surrounding community. The etiologies and anatomical sources of sinus pain were varied among subjects. A group of 38 subjects were randomly selected via block randomization to use the ClearUP Sinus Relief device. Subjects read the draft labeling that accompanied the device and without help from staff proceeded to self-perform the treatment.

Control subjects, totaling 33 subjects, followed the same procedure but used a sham/placebo device that appeared and functioned like the active device (*i.e.,* indicator lights and haptic vibration) but without emitting alternating current. The subjects and study staff were blinded to the device used.

At 10 minutes following stimulation, subjects completed the Modified NOSE to quantify congestion before and after treatment.

[1] Stewart, Weaver, Witsell, Yueh, Hannley and Johnson, "Outcomes after nasal septoplasty: results from the Nasal Obstruction Septoplasty Effectiveness (NOSE) study." Otolaryngology–Head and Neck Surgery, vol. 130, no. 3, pp. 283-290.

### INCLUSION CRITERIA

- 18 years of age and older
- Present with symptoms of sinus pain
- Have an initial sinus pain score of 4 or more on the visual analogue scale
- Be able to read and understand English
- Agree to participate in the study
- Be able and willing to provide Informed Consent

### EXCLUSION CRITERIA

- Do not meet Inclusion Criteria
- Have currently a dental infection
- Have currently abnormal cranial nerve or other neurological findings or symptoms that would require prompt medical attention
- Currently pregnant
- Have implanted electrostimulation devices including a pacemaker, a DBS, or a cochlear implant

### CONCOMITANT THERAPY

Of the 71 subjects, (b) (4) were recruited and received a pre-rhinoscopy intranasal spray composed of (b) (4) one to three hours before study screening and enrollment. Since the subjects were randomized, there was an even distribution of subjects that received intranasal spray in both active (b) (4) and sham groups (b) (4) effectively factoring out the effect of intranasal spray m the effect of the treatment with ClearUP Sinus Relief device.

### EFFECTIVENESS VARIABLES

The effectiveness variable was the change in the modified NOSE score before versus after treatment. Additional outcomes focused on usability of the device and preference compared with the current treatment options.

### STUDY SUBJECTS

All 71 study subjects that were enrolled completed the study.

### BASELINE CHARACTERISTICS

The mean age for the sham subjects was (b) (4) and for the active subjects (b) (4) Table 3). There was not a statistically significant difference in age between the (b) (4) groups ((b) (4) -sided t-test; $p = 0.7666$).

*Table 3 Subject Age*

| | Sham | Active |
|---|---|---|
| (b) (4) | | |

Both groups had approximately (b) (4) ratio of females to males (Table 4). There was not a statistically significant difference in the proportion of females between groups (Fisher's exact test (b) (4) .

*Table 4 Subject Sex*

| | Sham | | Active | |
|---|---|---|---|---|
| | N | % | N | % |
| **Female** | (b) (4) | | | |
| **Male** | | | | |

Both groups had a heterogeneous collection of etiologies, including previous diagnosis with chronic rhinosinusitis, allergic rhinitis, current infection, symptoms from barometric pressure change, and acute sinusitis (Table 5). Allergic rhinitis and chronic rhinosinusitis were the most commonly cited etiologies.

*Table 5 Sinus Pain Etiology. Note that subjects reported one or more etiology.*

| | Sham | | Active | |
|---|---|---|---|---|
| | N | % | N | % |
| **Chronic Rhinosinusitis** | (b) (4) | | | |
| **Allergic Rhinitis** | | | | |
| **Infection** | | | | |
| **Barometric Pressure** | | | | |
| **Acute Sinusitis** | | | | |
| **Unknown** | | | | |

Subjects described the location of their sinus pain as in the face over their cheeks, on the forehead above the eyes, between the eyes, and behind the nose. This collection of locations is consistent with pain and pressure originating in the paranasal sinuses.

## Analysis of Effectiveness

### Endpoints

The average Modified NOSE score reduction for all 71 subjects was (b) (4) for the active device condition and (b) (4) for the sham device condition. The difference in the mean NOSE reduction score between active- and sham-treated subjects was (b) (4) but it did not

reach statistical significance at the (b) (4) level (b) (4) (b) (4)-sided Mann-Whitney test[2]). The statistically insignificant result may be attributed to the fact that the changes in congestion in subjects with mild symptoms are expected to be more difficult to quantify.

The average Modified NOSE score reduction with four cut-off points (i.e. data from subjects with Modified NOSE (b) (4) before treatment) were evaluated as post-hoc analyses.

When the data for the subjects enrolling with moderate to severe congestion were considered (i.e., subjects showed Modified NOSE (b) (4), a significant effect of the active device treatment was found. Note that Modified Nose (b) (4) indicates the moderate to severe level of congestion shown in the Indications for Use for the ClearUP Sinus Relief device. There were total (b) (4) subjects ((b) (4) Sham subjects and (b) (4) Active subjects) in this study who met this cutoff value and they had at least a moderate problem with one or more of the following: congestion or stuffiness, nasal blockage or obstruction, or trouble breathing through nose. The Modified NOSE cutoff of (b) (4) or greater is further justified by a (b) (4)-person study that found that subjects with moderate congestion symptoms had a range of (b) (4) points on the full NOSE questionnaire, which is equivalent to (b) (4) points on the modified NOSE[3].

Table 6 shows the dada for the sham control group and the active treatment group who had moderate to severe congestion at enrollment (i.e., Modified Nose (b) (4). For this group of subjects, the average pre-treatment Modified NOSE scores were (b) (4) for the Sham and Active groups, respectively. The pre-treatment congestion scores had similar distributions in the (b) (4) groups with no statistically significant difference ((b) (4), (b) (4) sided Mann-Whitney test) between groups. The average post-treatment congestion scores were (b) (4) for the Sham and Active groups, respectively. The post-treatment congestion scores had similar distributions in the (b) (4) groups with no statistically significant difference (b) (4), (b) (4)-sided t-test) between groups.

***Table 6 Pre-treatment and Post-treatment Modified NOSE ≥ 5 Congestion Scores***

| | Device | N | Mean | S.D. | Lower 95% | Upper 95% |
|---|---|---|---|---|---|---|
| (b) (4) | | | | | | |

*Data from the subjects with Modified NOSE (b) (4) before treatment; S.D., Standard Deviation*

The average Modified NOSE score reduction for subjects using the active device was (b) (4) (Table 7). Here, (b) (4) of (b) (4) active-treated subjects (70%) exhibited a Modified NOSE reduction of (b) (4) points or more. The average Modified NOSE score reduction for subjects using the sham device was (b) (4) The difference in mean reduction between active- and

[2] The D'Agostino & Pearson normality test was used for all comparison groups. (b) (4) tailed unpaired t-tests were used for data with a normal distribution. (b) (4) ailed Mann-Whitney tests were used where at least one of the comparison groups exhibited a non-normal distribution.

[3] Lipan and Most, "Development of a severity classification system for subjective nasal obstruction." *JAMA Facial Plastic Surgery*. Vol. 15, no. 5, pp. 258-361, 2013.

sham-treated subjects was (b) (4), which reached the statistical significance ((b) (4) (b) (4)-sided Mann-Whitney test).

*Table 7 Modified NOSE Congestion Score Reduction for the subjects with NOSE (b) (4) before treatment*

| | Sham | Active | Difference | p-value† |
|---|---|---|---|---|
| (b) (4) | | | | |

**TREATMENT PREFERENCE**

Subjects treated with ClearUP Sinus Relief and the sham device were asked "Would you prefer the ClearUP Sinus Relief device to your current way of treating pain in your sinuses?" and "Do you think that the ClearUP Sinus Pain Relief is appropriate for treating your sinus pain?" 82% of subjects preferred ClearUP Sinus Pain Relief to their current treatment and 87% found the therapy is appropriate for treating their sinus pain. Sham-treated subjects also reported that they preferred the sham device to their current sinus pain treatment (91%) and found it appropriate for treatment (86%), which may be attributable to the therapeutic effect of the haptic feedback emitted by the sham device, preference for non-drug treatment options, and placebo response.

*Table 8 Treatment Preference*

| | Sham | | Active | |
|---|---|---|---|---|
| | n/N | % | n/N | % |
| (b) (4) | | | | |

**INSTRUCTIONS AND USABILITY**

A five-point scale was used to collect responses from subjects on the ease of self-training and of understanding the accompanying draft labeling. With the exception of (b) (4) to (b) (4) subjects, the large majority responded that they found the product easy to understand and that the instructions were easy to follow and well-illustrated. Additionally, the majority of subjects found the treatment itself to be easy and fast.

*Table 9 Instructions and Usability*

| | Strongly agree | Agree | Neutral | Disagree | Strongly Disagree | Total |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | |
| **Product is Easy to Understand** | 47<br>66.2% | 19<br>26.8% | 2<br>2.8% | 1<br>1.4% | 2<br>2.8% | 71 |
| **Instructions are Easy to Follow** | 47<br>66.2% | 20<br>28.2% | 0<br>0% | 3<br>4.2% | 1<br>1.4% | 71 |
| **Instructions are Well Illustrated** | 51<br>71.8% | 16<br>22.5% | 0<br>0% | 2<br>2.8% | 2<br>2.8% | 71 |
| **Performing Treatment is Easy** | 53<br>74.6% | 16<br>22.5% | 0<br>0% | 1<br>1.4% | 1<br>1.4% | 71 |
| **Performing Treatment is Fast** | 39<br>54.9% | 24<br>33.8% | 3<br>4.2% | 3<br>4.2% | 1<br>1.4% | 71 |

*N = 71 (33 for the sham condition; 38 for the active device condition)*

## SAFETY EVALUATION

In Clinical Study 1, subjects were asked about their experience using the device and notes were taken of any complications that were a result of the treatment. There were no serious adverse events observed during the study. Out of 38 subjects that self-treated with the active device, there was one case of minor transient facial erythema, which completely dissipated after 15 minutes. No other side effects of treatment were observed. Based upon these results, ClearUP Sinus Relief appears to be safe and well-tolerated for treating congestion.

## DISCUSSION

Subjects had a variety of sinus symptom etiologies including previous diagnosis of allergic rhinitis and chronic rhinosinusitis. After a single treatment, active-treated subjects who enrolled with moderate or severe congestion (Modified NOSE (b) (4) exhibited a statistically significant greater mean reduction in congestion than the subjects using the sham device.

For this group of subjects who demonstrated moderate or severe congestion (as in the Indications for Use for the subject device), the mean reduction in Modified NOSE score for the active-treated subjects was (b) (4) Stewart et al. (2004) showed that a NOSE score reduction (for the five questions) of (b) (4) points or greater indicates a clinically meaningful improvement in symptom severity. Since the Modified NOSE removed (b) (4) questions from the five-item questionnaire, the Modified NOSE minimum clinically meaningful difference (MCMD) would be approximately (b) (4) points or greater (b) (4) MCMD for the NOSE). Note that (b) (4) of the (b) (4) subjects (70%) from Study 1 exhibited a Modified NOSE score reduction of (b) (4) points or more, indicating a clinically meaningful effect for the majority of subjects.

In Study 1, a majority of active-treated subjects reported that they preferred ClearUP Sinus Relief to their current treatment (81.6%) and found that the ClearUP Sinus Relief was appropriate for treating their sinus symptoms (86.5%). Moreover, active-treated subjects tolerated the treatment very well and there was only one minor occurrence of transient facial erythema.

The NOSE self-report instrument in Study 1 was administered only after the treatment using the subject device. The uncertainty of the efficacy caused by this design was offset by the

fact that Study 1 was a randomized, double-blind controlled trial and ClearUP-treated subjects with moderate to severe congestion reported a significantly greater congestion symptom relief when compared to the sham-treated subjects. Furthermore, several peer-reviewed studies[4][5][6] have concluded that subjects can accurately recall symptom severity from up to four weeks ago, whereas the baseline data in Study 1 were collected on congestion symptom severity based on the subjects' recollection of only 10 minutes prior (before treatment with the device) to the treatment.

This randomized, double-blinded, sham-controlled trial demonstrates that the ClearUP Sinus Relief device is safe and effective in providing temporary relief of moderate to severe congestion.

## CONGESTION CLINICAL STUDY 2 - CLEARUP LONGITUDINAL STUDY

### STUDY OBJECTIVE

In Clinical Study 2, subjects with sinus symptoms for at least one month were given the ClearUP Sinus Relief device and were followed for 4 weeks while they treated themselves at home. Note that no subjects in Study 1 participated in Study 2.

Endpoints included the following:

- weekly changes in sinus pain (numeric rating scale)
- congestion (congestion quantifier 7, nasal obstruction symptom evaluation), and
- medication use, and user experience.

### STUDY DESIGN

A single-arm (N=(b) (4)), open label study was performed. Validated questionnaires were used to quantify sinonasal symptoms including pain (numeric rating scale) and congestion (Congestion Quantifier 7[7] (CQ7), NOSE, sinonasal outcome test 22), medication use, and user experience. Subjects used the ClearUP device for five minutes during the study visit and then took the device home with them with instructions to use the device once daily and up to four times daily as needed, with each treatment lasting five minutes.

Data on pain, congestion, and medication use was collected weekly for four weeks. Study visits took place at enrollment and at 4 weeks.

### INCLUSION CRITERIA

- 18-71 years of age
- Present with symptoms of sinus pain or facial pain in the forehead, periorbital, facial, or nasal region

[4] Salovey, Smith, Turk, Jobe, and Willis. "The Accuracy of Memory for Pain", Journal of Pain, 2(3):184-191, 1993
[5] Bolton, Humphreys, van Hedel. "Validity of weekly recall ratings of average pain intensity in neck pain patients", J Manipulative Physiol Ther. 2010 Oct;33(8):612-7.
[6] Singer, Kowalska, Thode. "Ability of patients to accurately recall the severity of acute painful events", Acad Emerg Med. 2001 Mar;8(3):292-5.
[7] D. E. Stull, J. Krouse, E. O. Meltzer, L. Roberts, S. Kim and L. Frank, "Development and Validation of the Congestion Quantifier Seven-Item Test (CQ7): A Screening Tool for Nasal Congestion," *Value in Health,* vol. 10, no. 6, pp. 457-465, 2007

- Current sinus/facial pain score (b) (4) (Numeric Rating Scale 0-10)
- Frequency of sinus/facial pain at least twice weekly for 1 month
- Able to read and understand English
- Agree to participate in the study
- Able and willing to provide Informed Consent

**EXCLUSION**

- Do not meet Inclusion Criteria
- Currently taking or recently taken any oral steroid medications in the last 90 days
- Sinus surgery in previous 90 days
- History of Chronic Migraine (≥ (b) (4) headache days per month)
- Pain location in the vertex, occiput, or temporal region of the skull or in mandibular region
- Purulent rhinorrhea
- Current dental infection
- Cranial nerve pathology (trigeminal neuralgia, facial nerve paralysis, etc.)
- Primary pain disorder (fibromyalgia, chronic regional pain syndrome, etc.)
- Implanted electrostimulation devices including a pacemaker, a DBS, or a cochlear implant

**TREATMENT AND CONTROL GROUPS**

All 30 subjects were treated with active ClearUP Sinus Relief in a single-arm, open-label study. Data from Study 2 were considered as further evidence, in addition to the data from Study 1, that the subject device is both well-tolerated and effective for reducing congestion symptoms in a real-world setting like the home.

**CONCOMITANT THERAPY**

To facilitate a real-world pragmatic trial, subjects were allowed to use medication during the study. However, the subjects who currently taking or recently took oral steroid medication were excluded from the study.

**EFFECTIVENESS VARIABLE**

Effectiveness variables included weekly change in sinonasal symptoms using the NOSE questionnaire, CQ7, and the sinonasal outcome test. Note that the NOSE questionnaire was administered at enrollment (i.e., before treatment) and after four weeks of treatment with ClearUP Sinus Relief device. In addition, data on medication use was collected weekly, and data on user experience was collected at the end of the study.

**STUDY SUBJECTS**

All (b) (4) study subjects that were enrolled completed the study.

**BASELINE CHARACTERISTICS**

*Table 10 Subject Age*

| | |
|---|---|
| **N** | 30 |
| **Mean** | 43.58 |
| **95% CI** | (38.9, 47.9) |
| **Min** | 23 |
| **Max** | 71 |
| **Median** | 40.5 |

*Table 15 Subject Sex*

| | N | % |
|---|---|---|
| **Female** | 21 | 70% |
| **Male** | 9 | 30% |

Study subjects had a heterogeneous collection of etiologies (Table 12) including previous diagnosis with allergic rhinitis, nasal polyps and cysts, and undiagnosed causes.

*Table 12 Sinus Pain Etiology. Note that subjects reported one or more etiology*

| | N | % |
|---|---|---|
| **Allergic Rhinitis** | 11 | 36.7 |
| **Nasal Polyp** | 1 | 3.3 |
| **Nasal Cyst** | 1 | 3.3 |
| **Undiagnosed Cause** | 17 | 56.7 |

## ANALYSIS OF EFFECTIVENESS

### ENDPOINTS

For subjects who enrolled with congestion that was moderate to severe (b) (4) average congestion score at enrollment was (b) (4) (Table 13). The average post-treatment congestion scores were (b) (4) at week 1, (b) (4) eek 2, (b) (4) at week 3, and (b) (4) at week 4. Lower CQ7 scores indicate less congestion symptom severity. The differences in congestion score from enrollment were (b) (4) at week 1, (b) (4) at week 2, (b) (4) at week 3, and (b) (4) at week 4. At all time points, the magnitude of reduction in congestion from enrollment was statistically significant. At week 4, 21 of 24 subjects (88%) exhibited a CQ7 score reduction of three points or greater.

*Table 13 Weekly Congestion Scores (Congestion Quantifier 7)*

| | Mean | S.D. | Lower 95% | Upper 95% | Difference | % Change | p-value |
|---|---|---|---|---|---|---|---|
| **Enrollment** | (b) (4) | | | | | | |
| **Week 1** | | | | | (b) (4) | | |
| **Week 2** | | | | | | | |
| **Week 3** | | | | | | | |
| **Week 4** | | | | | | | |

*Data from subjects with CQ7 > 15 before treatment (N = 24), S.D., Standard Deviation, p-value is from (b) (4) -tailed paired t-test compared with enrollment*

Table 14 displays congestion data (CQ7) from all subjects.

***Table 14 Weekly Congestion Scores (CQ7)***

| | Mean | S.D. | Lower 95% | Upper 95% | Difference | p-value |
|---|---|---|---|---|---|---|
| **Enrollment** | (b) (4) | | | | | |
| **Week 1** | | | | | (b) (4) | |
| **Week 2** | | | | | | |
| **Week 3** | | | | | | |
| **Week 4** | | | | | | |

*Data from all subjects (N = (b) (4) regardless of their baseline CQ7 scores, S.D., Standard Deviation, p-value is from (b) (4)-tailed paired t-test compared with enrollment*

Table 15 shows the 5-item NOSE scores. The average NOSE was (b) (4) at enrollment and (b) (4) at week 4. The difference in score between enrollment and week 4 was (b) (4) This magnitude of difference (b) (4) was statistically significant, but it was less than the MCMD of (b) (4) for the 5-item NOSE questionnaire (Stewart et al., 2004).

***Table 6 Monthly Congestion Scores (5-item NOSE)***

| | Mean | S.D. | Lower 95% | Upper 95% | Difference | p-value |
|---|---|---|---|---|---|---|
| **Enrollment** | (b) (4) | | | | | |
| **Week 4** | | | | | | |

*Data from all subjects (N = (b) (4), S.D., Standard Deviation, p-value is from (b) (4)-tailed paired t-test compared with enrollment*

When the subjects with moderate to severe congestion (Modified NOSE ≥ (b) (4) were considered that are consistent with the Indications for Use for the ClearUp Sinus Relief device, the average congestion score was (b) (4) at enrollment and (b) (4) at week 4 (Table 16). The difference in score between enrollment and week 4 was (b) (4) and this magnitude of difference was statistically significant. Furthermore, this difference is greater than the MCMD of (b) (4) for the Modified NOSE.

***Table 7 Monthly Congestion Scores (3-item Modified NOSE)***

| | Mean | S.D. | Lower 95% | Upper 95% | Difference | p-value |
|---|---|---|---|---|---|---|
| (b) (4) | | | | | | |

*Data from subjects with Modified NOSE (b) (4) at enrollment (N = (b) (4)), S.D., Standard Deviation, p-value is from (b) (4)-tailed paired t-test compared with enrollment*

Table 17 shows that Sinonasal Outcome Test 22[8] result at enrollment was (b) (4) The average post-treatment sinus symptom scores were (b) (4) at week 2 and (b) (4) at week 4. The differences in sinus symptom score from enrollment were (b) (4) at week 2 and (b) (4) at week 4. At all timepoints, the magnitude of reduction in sinus symptoms from enrollment was statistically significant.

[8] Hopkins, Gillett, Slack, Lund and Browne, "Psychometric validity of the 22-item Sinonasal Outcome Test," *Clinical otolaryngology,* vol. 34, no. 5, pp. 447-454, 2009.

*Table 8 Bi-Weekly Sinus Symptoms (Sinonasal Outcome Test 22)*

| | Mean | S.D. | Lower 95% | Upper 95% | Difference | p-value |
|---|---|---|---|---|---|---|
| **Enrollment** | (b) (4) | | | | | |
| **Week 2** | | | | | (b) (4) | |
| **Week 4** | | | | | | |

*S.D., Standard Deviation, p-value is from* (b) (4) *-tailed paired t-test compared with enrollment (N =* (b) (4)

Subjects completed a weekly medication diary (Table 18), detailing whether they were taking the following classes of medications: pain, nasal decongestant spray, nasal steroid spray, decongestant in pill form, antihistamine, or prescription antibiotics. A trend was observed in which subjects took fewer different types of medication (Mean # of Medications) over the course of the four weeks of treatment and a smaller percentage of subjects reported taking one or more medication.

*Table 9 Weekly Medication Use (Medication Diary)*

| | Mean # of Medications | Subjects on Medications |
|---|---|---|
| **Enrollment** | (b) (4) | |
| **Week 1** | | |
| **Week 2** | | |
| **Week 3** | | |
| **Week 4** | | |

N (b) (4)

### SELF-REPORT OF DURATION OF SYMPTOM RELIEF

At the end of the four-week trial, subjects (N = (b) (4) were asked to complete a questionnaire about their experience with the study device. When asked about the average duration of sinonasal symptom relief after using the study device, subjects reported that their relief lasted: 6 hours or more (16.6%), 5-6 hours (20%), 3-4 hours (23.3%), 1-2 hours (10%), less than 1 hour (16.6%), and no relief (13.3%).

### USER EXPERIENCE

Subjects (N = (b) (4) were asked about their experience using the ClearUP Sinus Relief device at the end of the four-week trial[9]. 73% of subjects reported that they were somewhat or extremely satisfied using the device, 73% reported that they preferred using ClearUP Sinus Relief to their current methods for treating sinonasal symptoms, and 77% of subjects reported that they would probably or definitely recommend the device to others with sinus symptoms. When the subjects were asked to elaborate about their experience, they reported that they had "reduced the number of symptom days", the device promoted "improved breathing", the device improved the ability "to get work done," "exercise," "rest," and enhanced "wellbeing."

[9] The questions included: "Overall, how satisfied are you with the ClearUP device after using it? Why?", "Do you prefer the ClearUP device to your current way of treating sinus pain? Why?", "Would you add ClearUP to your current sinus treatment regimen?", "Would you recommend ClearUP to others that have sinus pain?", "In the last week, after a five-minute ClearUP treatment, for approximately how long do you have symptom relief?", "Have you experienced any noticeable feelings or changes in appearance or functioning that may be related to your use of the ClearUP device?", "Did these changes occur during use of the ClearUP device, afterwards, or both?", and "Did these changes eventually go away on their own?"

## SAFETY EVALUATION

In Study 2, subjects were asked about their experience using the device and notes were taken of any complications that were a result of treatment. There were no serious adverse events observed during the study. Out of 30 subjects that self-treated with the device, there were (b) (4) reports of minor transient facial erythema, one report of eyelid twitch, and one report of headache. No other side effects of treatment were observed. Based upon these results, ClearUP Sinus Relief appears to be safe and well-tolerated for the relief of congestion.

## DISCUSSION

Study 1 demonstrated that ClearUP can relieve sinus pain and congestion and the reduction in symptoms was greater than the placebo effect. In Study 2, ClearUP Sinus Relief was used in office to establish the baseline data and for four weeks at home. Subjects reported increasing and statistically significant reductions in congestion over weeks 1-4 of treatment. For subjects who enrolled with moderate to severe congestion, mean reductions in CQ7 score were (b) (4) at week 1, (b) (4) at week 2, (b) (4) at week 3, and (b) (4) at week 4. Previous studies have concluded that a CQ7 score reduction of three points[10] or greater indicates a clinically meaningful improvement in symptom severity. At week 4, 21 of (b) (4) subjects (88%) exhibited a CQ7 score reduction of three points or greater, indicating a clinically meaningful reduction in symptom severity for the great majority of subjects. Side effects of treatment were minor and included transient facial erythema, eyelid twitch, and headache.

Study 2 was an open-label 4-week study and did not have a control group. To mitigate the uncertainty of effectiveness created by this design, a thorough literature review was performed to identify the magnitude of placebo effect in subjects with congestion that completed the CQ7 questionnaires. The literature search identified (b) (4) peer-reviewed papers[11,12,13], which used the CQ7 as an instrument and the sham control. An analysis of these (b) (4) papers indicated that the mean percent changes in CQ7 score for placebo-treated subjects were -27% and -20% in the (b) (4) studies that were identified in the literature search. This range of CQ7 score reductions in the (b) (4) papers is smaller than the mean percent CQ7 score reduction reported in Study 2 (-44%), indicating that the ClearUp Sinus Relief device's effectiveness above and beyond the placebo effect.

Furthermore, Study 2 was a 4-week study that demonstrated week after week improvements over the 4 weeks in congestion symptom severity, indicating a gradual and accumulating benefit. The extent of uncertainty for the risk associated with a lack of efficacy of ClearUP Sinus Relief is low given that (b) (4) separate clinical studies (i.e., Study 1 and Study 2) with

[10] Stull, Vernon, Canonica, Crespi and Sandor, "Using the Congestion Quantifier Seven-Item Test to assess change in patient symptoms and their impact.," *In Allergy & Asthma Proceedings,* vol. 29, no. 3, 2008

[11] Schenkel, Ciesla, & Shanga. (2018). Effects of nasal dilator strips on subjective measures of sleep in subjects with chronic nocturnal nasal congestion: a randomized, placebo-controlled trial. *Allergy, Asthma & Clinical Immunology*, *14*(1), 34

[12] Katotomichelakis, Van Crombruggen, … and Kastanioudakis, I. (2017). A herbal composition of Scutellaria baicalensis and Eleutherococcus senticosus shows vasocontrictive effects in an ex-vivo mucosal tissue model and in allergic rhinitis patients. *Clinical Phytoscience*, *3*(1), 21.

[13] The limitation of Schenkel et al. study is lack of statistical power analysis to calculate the necessary number of subjects to detect an effect. Also, the authors mentioned that the study is an exploratory. Therefore, the study was not statistically powered to accurately measure the placebo effect. The Katotomichelakis et al. study investigated the effect of an herbal nasal spray (as an alternative to pharmacotherapy) for relieving patients' nasal congestion. The mechanism of the action in this study is different from the ClearUp Sinus Relief device. Therefore, the placebo effect in this study may not be identical to the ClearUp Sinus Relief studies.

completely different study subjects provided evidence of ClearUP safety and efficacy in reducing congestion. Uncertainty of risk is further reduced by the fact that congestion is not a life-threatening disease and it can be treated with over the counter or prescription drugs.

The majority of subjects reported that they were satisfied with their experience of using the subject device and would recommend it to others with sinus symptoms. These data indicate the ClearUP Sinus Relief device can safely and effectively relieve moderate to severe congestion.

**CONCLUSION**

The data presented for Clinical Study 1 demonstrated that the ClearUP Sinus Relief reduced congestion significantly greater than the sham treatment in subjects with moderate to severe congestion. The mean change of (b) (4) in congestion score (Modified NOSE) was greater than the established minimum clinically important difference (i.e., (b) (4) ). The data presented for Clinical Study 2 demonstrate that ClearUP treatment over four weeks, significantly reduced self-reported congestion using the CQ7 measure in subjects with moderate to severe congestion. The mean change of (b) (4) in congestion CQ7 score was greater than the established minimum clinically important difference of 3. Additionally, ClearUP Sinus Relief treatment over four weeks resulted in a significant reduction in the modified NOSE score (b) (4) ), and this reduction was greater than the established minimum clinically important difference (b) (4) Combined, (b) (4) studies using different validated measures of congestion demonstrated a clinically meaningful improvement in congestion symptoms for subjects with moderate to severe symptoms. Data from both studies indicated that ClearUP Sinus Relief has an excellent safety profile with few occurrences of minor side effects. By comparison, the side effect profile of drugs commonly used for treating congestion may include epistaxis, dizziness, nausea, insomnia, tachycardia, and syncope. Overall, these results support our conclusion that ClearUP Sinus Relief safely and effectively reduces moderate to severe congestion.

The primary benefits were:

- Clinically meaningful relief of congestion symptoms
- Improved patient satisfaction
- Reduced reliance on medication
- Excellent safety profile

Pediatric Extrapolation

The ClearUP Sinus Relief device is indicated for patients age 18 and older. For medical devices, the FD&C Act defines patients before their 22nd birthday as pediatric patients. In this De Novo request, data from patients under 22 were used to support the use of the device in patients over the age of 18. It was appropriate to indicate the device for individuals 18 and older because patients aged 18 to 21 do not carry additional risks relative to the patient population studied.

## LABELING

The ClearUP Sinus Relief labeling is sufficient and meets labeling requirements for over-the-counter devices. It contains the indication for use, limitation, contraindication, device description, maintenance, warning, caution, instruction for use, summary of clinical trials, information related to electromagnetic compatibility, expected device life, environmental operating conditions, electrical specifications, and symbols and markings.

## RISKS TO HEALTH

Table 19 identifies the risks to health that may be associated with the use of a transcutaneous electrical nerve stimulator for the relief of congestion and the measures necessary to mitigate these risks.

***Table 10. Identified Health Risks and Mitigation Measures***

| Identified Risk | Mitigation Measures |
|---|---|
| Injury from electrical current on face causing one or more of the following:<br>• Skin burn<br>• Skin redness<br>• Skin irritation<br>• Facial muscle twitching<br>• Electrical shock<br>• Pain<br>• Headache<br>• Discomfort or muscle twitching of the eye | Non-clinical performance testing<br>Human factors testing<br>Software verification, validation, and hazard analysis<br>Electrical safety testing<br>Electromagnetic compatibility testing<br>Battery safety testing<br>Labeling |
| Nerve and muscle injury | Non-clinical performance testing<br>Electrical safety testing<br>Software verification, validation, and hazard analysis |
| Ineffective treatment leading to worsening congestion | Labeling |

## SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the transcutaneous electrical nerve stimulator for the relief of congestion 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, including electrical stimulation parameters that must be specified and verified.
2. Performance data must demonstrate the electromagnetic compatibility, battery safety, and electrical safety of the device.
3. Software verification, validation, and hazard analysis must be performed.
4. The patient-contacting components of the device must be demonstrated to be biocompatible.

5. Human factors testing must demonstrate that users can successfully use the device in the intended use environment based solely on its labeling and instructions for use.
6. Labeling must include the following:
    a. Instructions for use, including images that demonstrate how to use the device;
    b. Device specifications, including the number of channels, output waveform, stimulation peak voltage and current, pulse duration, frequency, maximum current density, maximum phase charge, and power source; and
    c. Explanations of the user-interface components.

## BENEFIT-RISK DETERMINATION

Data from non-clinical testing as well as clinical studies demonstrate that the risks of the use of ClearUP Sinus Relief for the temporary relief treatment of moderate to severe congestion are outweighed by the benefits to health and quality of life.

Clinical studies indicate that ClearUP Sinus Relief is well-tolerated with few occurrences of minor side effects all of which resolved on their own (Study 1: 1 report (2.6%) of skin erythema; Study 2: 2 reports (6.7%) of skin erythema, 1 report (3.3%) of headache, 1 report (3.3%) of muscle twitch).

The probable benefits of ClearUP Sinus Relief are based upon clinical studies. Study 1 demonstrated that ClearUP provided a clinically meaningful reduction in congestion symptom severity acutely at 10 minutes after treatment for a majority (70%) of subjects. Study 2 demonstrated that after 4 weeks of use, 88% of subjects experience a clinically meaningful reduction in congestion severity.

Additional factors to be considered in determining benefits and risks include uncertainty in the results of Study 1 due to the administration of the congestion instrument only after treatment. This uncertainty is offset by the controlled double blind trial design and previous studies that indicate patient recollection of symptoms is reliable. Also, Study 2 was an open-label 4-week study and did not have a control group. The uncertainty created by this design is addressed by a literature search discussed above. The extent of uncertainty for the risk associated with a lack of efficacy of ClearUP is low given that (b) (4) separate clinical studies with different study subjects provided evidence of ClearUP safety and efficacy in reducing congestion.

Currently, medications are the only FDA-approved approaches available for treating congestion at home. ClearUP Sinus Relief is a device that provides temporary relief of moderate to severe congestion. Importantly, ClearUP is very well tolerated, non-pharmacological device with few reports of minor side effects, making it a useful addition to the armamentarium for treatment of nasal congestion. This is notable when contrasted with the side effect profile of drugs commonly used for treating congestion.

The usability and the clinical studies results indicate that the users can comprehend the device labeling and effectively use the device.

When subject to general and special controls, the probable benefits to health by using the ClearUP Sinus Relief for its intended use outweigh the risks of probable injury or illness (e.g., transient facial erythema, eyelid twitch, and headache) related to the ClearUP Sinus Relief.

Patient Perspectives

Patient perspectives considered for the ClearUP Sinus Relief included:

- Assessment of patients' impression of improvements
- Patient feedback was collected via subject questionnaire at the end of Study 2

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that the benefits outweigh the risks of the ClearUP Sinus Relief. The device 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 ClearUP Sinus Relief is granted and the device is classified under the following:

Product Code: QNU
Device Type: Transcutaneous electrical nerve stimulator for the relief of congestion
Class: II
Regulation: 21 CFR 874.6000