

**DE NOVO CLASSIFICATION REQUEST FOR
SANA DEVICE**

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Audio-visual stimulator for pain relief. An audio-visual stimulator for pain relief is a device intended to deliver light stimuli to the eyes and sound stimuli to the ears to provide pain relief. This device is intended to be used adjunctively to other modes of therapy to relieve pain.

NEW REGULATION NUMBER: 21 CFR 890.5775

CLASSIFICATION: Class I

PRODUCT CODE: QYN

BACKGROUND

DEVICE NAME: Sana Device

SUBMISSION NUMBER: DEN250005

DATE DE NOVO RECEIVED: May 3, 2025

SPONSOR INFORMATION:

Sana Health
2051 Dogwood Street, Suite 220
Louisville, CO 80027

INDICATIONS FOR USE

The Sana Device is indicated as follows:

The Sana Device is indicated for patients aged 18 and older as an adjunct to other modes of therapy for temporary relief of neuropathic pain for use at home or in the clinic.

LIMITATIONS

The sale, distribution, and use of the Sana Device are restricted to prescription use in accordance with 21 CFR 801.109.

The device is not intended to be used as a stand-alone device.

This device is not for use by:

- Persons under the age of 18.
- Pregnant women.
- Persons with a history or presence of photo-sensitive epilepsy.
- Persons sensitive to light and/or sounds.
- Persons with a history or presence of condition(s) that may affect balance, such as seizure disorders, tinnitus or vertigo.
- Persons with eye and/or ear infection.
- Persons suffering from migraine headaches.
- Persons who are visually or hearing impaired (deaf), including those with a significant difference in hearing between ears or sight between eyes.

In the clinical study of the device, the primary and secondary endpoint results were presented for both the intent-to-treat (ITT) population (i.e., all randomized subjects) and the per-protocol (PP) population (i.e., subjects who were randomized, completed the baseline, week 2, week 10, and week 14 assessments, and did not have major any protocol deviations). In FDA's evaluation of the clinical study, while FDA relied on analyses from both the ITT and PP populations to come to a benefit-risk determination, the sample size for the PP population was not designed to evaluate differences in outcomes based on the etiology of neuropathic pain.

Also, participant compliance with device use was evaluated and reported. In FDA's evaluation of the clinical study, while adherence rates were not statistically different between groups, the sub-optimal adherence rates (i.e., 67% for the active group, 74% for the control group) could have contributed to the high amount of missing data observed, as well as the 8 total patients who withdrew during the study period.

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

DEVICE DESCRIPTION

The Sana Device is an externally worn mask that is designed to deliver a sequence of coordinated sounds and light, known as audiovisual stimulation (AVS). The AVS consists of coordinated pulses of light (through the user's closed eyelids) and sound (through commercially available headphones), cycling through 12 patterns at 3 separate frequencies. While the volume of sound and brightness of light is user-adjustable for comfort, the pattern of light and sound is fixed. The maximum sound level is limited to 60dB, while the maximum intensity of light is 35 LUX. Light therapy is transmitted at low frequency between 0.5Hz - 10Hz. The Sana mask also includes a heart rate variability (HRV) sensor, which is not used during therapy. Therefore, the safety and effectiveness of the HRV functionality was not reviewed as part of this submission, but the HRV sensor materials were evaluated for biocompatibility.



Figure 1: Image of the Sana Device

Therapy is delivered to the patient in 16-minute sessions. It is recommended to use the device twice per day, once during the day and another session before bed, but it may be used as often as the patient desires depending on the severity of their symptoms. The Sana Device is intended to be used as an adjunct treatment to other modes of therapy when relieving neuropathic pain. Therapy can be controlled through buttons on the headset or with an optional mobile application (app) which connects to the device via Bluetooth. The app also allows the user to log symptom information for informational purposes only.

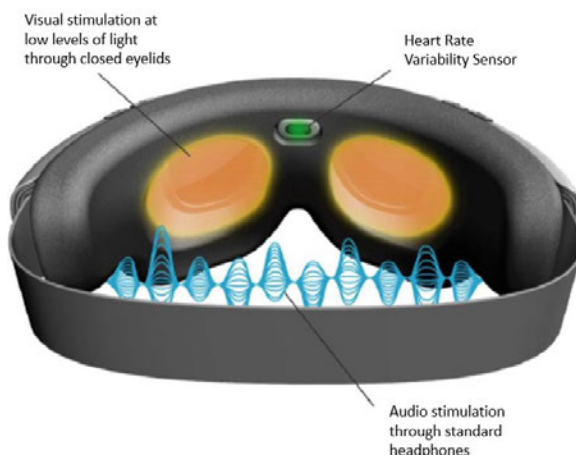


Figure 2: Image of the Sana Device

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The foam mask, head strap, and HRV sensor are considered patient-contacting components of the device. The foam mask is comprised of polyurethane foam covered with nylon cotton fabric, the head strap is comprised of nylon and spandex, and the HRV sensor is comprised of polycarbonate. All patient contacting components are categorized as surface contacting with long term contact duration (> 30 days cumulative use) of intact skin.

A biocompatibility evaluation was conducted in accordance with the International Standard ISO 10993-1: 2009 “Biological Evaluation of Medical Devices Part-1:

Evaluation and Testing Within a Risk Management Process.” According to the contact classification and duration of the patient-contacting materials, assessment of the device should include the following tests:

- Cytotoxicity (ISO 10993-5:2009)
- Sensitization Test (ISO 10993-10:2010)
- Intracutaneous Reactivity (ISO 10993-10:2010)

However, all patient contacting materials are included in Attachment G of FDA’s guidance document “Use of International Standard ISO 10993-1, ‘Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process’” as intact skin contacting materials with low biocompatibility risk. Considering that these materials have a history of safe use in medical devices, the total cumulative contact duration is low, and that the manufacturing process complies with Quality System Regulations (21 CFR 820.50, 21 CFR 820.80, 21 CFR 820.100, 21 CFR 820.198, and 21 CFR 803), biocompatibility data was not evaluated for the Sana Device.

Color additive Acid Black 172 is present in the head strap and foam mask materials. Because the device is long-term contacting (> 30 days cumulative use) with intact skin, a toxicological risk assessment was provided demonstrating that patient exposure to this color additive is at a tolerable level without risk of serious harm.

ELECTROMAGNETIC CAPABILITY & ELECTRICAL SAFETY

Electromagnetic compatibility (EMC) and electrical safety verification testing were conducted to confirm the EMC and electrical safety of the Sana Device. Testing was conducted in accordance with:

- IEC 60601-1: 2005, Medical Electrical Equipment – Part 1: General requirements for basic safety and essential performance.
- 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 60601-1-11, Medical Electrical Equipment – Part 1-11: General requirements for basic safety and essential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical equipment and medical electrical systems used in the home healthcare environment

The testing met the required performance standards.

Battery testing

The Sana Device is powered by a rechargeable lithium polymer battery, which complies with IEC 60601-1:2005 + A1:2012 and IEC 62133 Edition 2.0 2012-12 “Secondary cells and batteries containing alkaline or other non-acid electrolytes - safety requirements for portable sealed secondary cells, and for batteries made from them, for use in portable applications.”

MAGNETIC RESONANCE (MR) COMPATIBILITY

The Sana Device has not been tested for MR Compatibility and should not be used in an MR environment.

SOFTWARE

The device software includes embedded software within the mask. The software manages the AVS stimulation provided by the device.

All of the elements of software information for basic documentation as outlined in FDA's guidance document "Content of Premarket Submissions for Device Software Functions," issued June 2023 were provided.

The software documentation included in the De Novo request is in sufficient detail to provide reasonable assurance that the software will operate in a manner described in the specification.

PERFORMANCE TESTING - BENCH

Optical radiation safety testing was conducted according to ANSI Z80.36-2016 "American National Standard for Ophthalmics – Light Hazard Protection for Ophthalmic Instruments" to confirm the device meets the safety limits established by the standard. Sound safety testing was conducted to confirm the default and maximum volume settings meet safety specifications discussed in National Institute for Occupational Safety and Health (NIOSH) "Occupational Noise Exposure, Revised Criteria" (1998)¹ and World Health Organization (WHO) Report "Standard for Safe Listening Systems: Situational Analysis" (Feb. 2017)². All requirements were met.

Summative human factors testing and labeling validation were conducted which demonstrate minimal usability risk based upon the identified user tasks.

¹ NIOSH, *Criteria for a recommended standard: Occupational noise exposure, revised criteria 1998* (DHHS/NIOSH Pub. No. 98-126, June 1998), U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health

² Christian Bertin, *Standards for safe listening systems: situation analysis*. (World Health Organization, February 2017).

SUMMARY OF CLINICAL INFORMATION

The Sana Device was evaluated in a single-site, double-blinded, randomized, parallel-arm, sham-controlled clinical trial. The primary objective of this study was to assess the effectiveness of the Sana Device in managing neuropathic pain as an adjunct to other pain therapies.

The trial consisted of 75 subjects over the age of 18 with a clinical diagnosis of neuropathic pain and consistent medication use for at least 4 weeks prior to the first baseline visit. Patients were excluded from enrollment if they were diagnosed with photosensitive epilepsy, vision impairments impacting assessment of light in one or both eyes, deafness in one or both ears, psychiatric disorders, or eye or ear infection. Subjects were screened for inclusion/exclusion criteria and were randomly assigned to either a Sana Device treatment group (i.e., active group) or a sham group using a 1:1 ratio. Thirty-four (34) patients were assigned to the active group, while 41 patients were assigned to the sham group.

Once enrolled, subjects participated in a 2-week baseline period where the primary and secondary outcome measures were assessed at Week 0 and Week 2. Medical history, medication regimen, and other pain management techniques were also recorded during baseline. The intervention phase consisted of 8-weeks of home use (Week 2 through Week 10) where subjects used the device whenever they experienced pain during the day, as well as right before bedtime. The active group received the Sana device, while the sham group received a sham device designed to deliver a neutral AVS program. Sham programming was not intended to have the same therapeutic effects as the active Sana device, but it was designed to deliver a relaxing effect to maintain blinding and reduce dropouts due to lack of therapeutic effect. All device packaging, physical design, and directions for use were common to both groups. During the intervention phase, the primary and secondary endpoints were evaluated every two weeks. Compliance reminders were sent to subjects' cell phones, and the research team would engage with patients if their device compliance was below 70%. Device compliance for each participant was calculated as the percentage of days on which the participant used their assigned device at least once during the intervention phase. After the intervention phase, subjects stopped using the device and entered a 4-week follow-up phase (Week 10 to Week 14) where final assessments were taken at Week 14.

The primary endpoint defined for this study was the mean difference between active and sham groups after 8 weeks of treatment and 4 weeks of follow-up on the Neuropathic Pain Symptom Inventory (NPSI) total score. Secondary endpoints included the mean difference between active and sham groups after 8 weeks of treatment and 4 weeks of follow-up on the Generalized Anxiety Disorder-7 (GAD-7), Patient Health Questionnaire-9 (PHQ-9), Pittsburgh Sleep Quality Index (PSQI), and Patient Global Impression of Change Quality of Life (PGIC-QOL) scales. The safety endpoint was the rate of treatment emergent adverse events, which were defined as adverse events occurring after first use of the active or sham devices. However, all adverse events, including those which occurred before the first use of the active or sham device, were recorded and analyzed. Subjects were instructed to report adverse events at check-in meetings, as well as proactively record them at home.

A summary of patient demographics is presented in Table 1 below.

Table 1: Patient Demographics

<u>Gender</u>	<u>Group</u>	<u>N</u>	<u>Mean (SD)</u>
All	Both	75	45.41 (14.35)
	Active	34	42 (12.71)
	Sham	41	48.24 (15.15)
Female (She/Her)	Active	27	43.63 (12.82)
	Sham	25	46.92 (14.89)
Male (He/Him)	Active	7	35.71 (10.9)
	Sham	16	50.31 (15.81)

Eight patients withdrew from the study either voluntarily or due to treatment emergent adverse events. Five patients withdrew from the active group: 2 patients withdrew voluntarily, 1 patient withdrew after a protocol deviation, and 2 withdrew after treatment emergent adverse events (increased pain and headache). Three patients withdrew from the sham group: 2 patients withdrew voluntarily, and 1 patient withdrew after a protocol deviation.

Results are reported for the Intent to Treat (ITT) and Per-Protocol (PP) populations, which are defined as:

- **Intent to Treat (ITT) population:** All participants who were randomized, including those with protocol violations or missing assessments that exclude them from the Per-Protocol (PP) analysis population.
- **Per-Protocol (PP) population:** Participants who were randomized, completed the Baseline, Week 2, Week 10, and Week 14 assessments, began treatment, and did not have any major protocol deviations. For the PGIC-QOL scale (secondary endpoint), participants needed to complete the Week 10 and Week 14 assessments to be included.

The study was not specifically powered for the PP population.

Table 2 presents the within group differences in NPSI total score for the active and sham groups from Week 2 to Week 14. The active group experienced an 11.7-point reduction for the ITT group and a 10.9-point reduction for the PP group, which are both statistically significant and clinically meaningful. The sham group saw a reduction of 2.94 points and 1.96 points for the ITT and PP groups respectively, which is not a statistically significant or clinically meaningful improvement.

Table 2: Within Group Change for the NPSI Total for the ITT and PP Populations

<u>Outcome</u>	<u>Group</u>	<u>Population</u>	<u>N</u>	<u>Mean Change (Standard Error)</u>	<u>T Ratio</u>	<u>P-Value</u>
NPSI Total	Active	ITT	34	11.704 (2.815)	4.16	<0.001
		PP	20	10.895 (3.346)	3.316	<0.001
	Sham	ITT	41	2.94 (2.511)	1.178	0.239
		PP	26	1.958 (2.924)	0.67	0.504

Results for the primary endpoint showed that the active group experienced a mean improvement of 8.75 points in NPSI total score compared to sham from Week 2 to Week 14. The difference

between groups is statistically significant and clinically meaningful. A minimally clinically important difference (MCID) of 8.19 points was calculated using the anchor method, in which the PGIC-QOL scale (secondary endpoint) was used as the anchor. A correlation coefficient of 0.32 was calculated between the NPSI and PGIC-QOLs, which indicates a sufficient relationship for this method. Results showing the difference between groups can be found in Table 3 below.

Table 3: Summary of Primary Endpoint Results (Difference in NPSI Total Between Groups) for the ITT and PP Populations

<u>Outcome</u>	<u>Population</u>	<u>N</u> <u>(Active)</u>	<u>N</u> <u>(Sham)</u>	<u>Mean Difference</u> <u>(Standard Error)</u>	<u>T Ratio</u>	<u>P-Value</u>
NPSI Total	ITT	34	41	8.75 (3.772)	2.319	0.021
	PP	20	26	8.936 (4.398)	2.032	0.043

Figure 3 and Table 4 below show the difference between groups in NPSI total score for each study visit. During the intervention phase (Week 2 through Week 10), both groups experienced a parallel reduction in NPSI total scores (active: 9.1-point reduction; sham: 9.9-point reduction). The difference in NPSI scores at Week 10 compared to baseline were clinically meaningful and statistically significant for both groups. However, during the follow-up phase, the active group continued to improve (2.57-point reduction) while the sham group worsened (6.96-point increase). Because the sham device was intended to provide a relaxation effect to maintain blinding, the sham group improved while receiving treatment. The difference between groups becomes apparent once device use is halted, which shows that the active Sana Device continues to provide pain relief for an additional four weeks compared to sham.

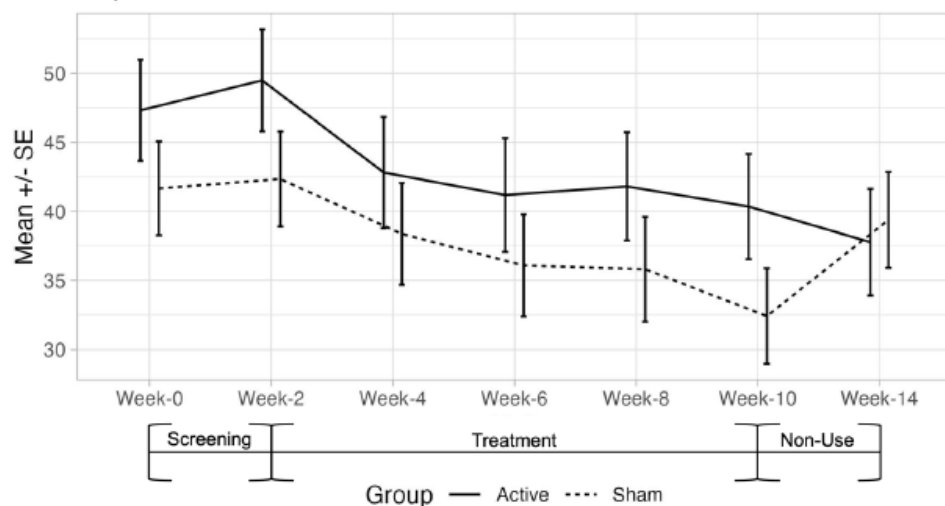


Figure 3: NPSI Total Score at each Study Visit for the ITT Population

Table 4: Change in NPSI Total Score for Active and Sham Groups

<u>Time Period</u>	<u>Group</u>	<u>Mean Change</u>	<u>SE</u>	<u>P-Value</u>	<u>Mean Difference</u> <u>(Active-Sham);</u> <u>P-Value</u>
	Active	9.1	2.7	<0.001	-0.78;

Treatment Period (Week 2 – Week 10)	Sham	9.9	2.5	<0.001	0.83
Non-Treatment Period (Week 10 – Week 14)	Active	2.57	2.85	0.37	9.53; 0.012
	Sham	-6.96	2.46	0.005	
Total Study Period (Week 2 – Week 14)	Active	11.7	2.8	<0.001	8.75; 0.021
	Sham	2.94	2.5	0.24	

A responder analysis was conducted using an MCID definition of 8.19 points. Based on this definition, 67% of active patients were responders, while only 32% of sham patients were responders.

Table 5: Responder Rate for NPSI Total Score

<u>Group</u>	<u>Responders</u>	<u>Non-Responders</u>
Active	14	7
Sham	9	19

Device adherence rates were similar between groups, which is shown in the table below. Sixty-seven percent (67%) of the active group were considered adherent whereas 74% of the sham group were adherent. The difference was not statistically significant.

Table 6: Device Adherence for Active and Sham Groups

<u>Group</u>	<u>N</u>	<u>Mean (SD)</u>
Both	75	71% (27%)
Active	34	67% (26%)
Sham	41	74% (27%)

In terms of safety, all adverse events captured during the study are listed in the table below. All reported adverse events were non-serious and resolved without long-term sequelae. Two treatment emergent adverse events were reported during the trial (i.e., increased pain and headache), both of which were attributed to the subject device. All adverse events were minor..

Table 7: Adverse Events

<u>Subject ID</u>	<u>AE</u>	<u>Relatedness</u>	<u>Prescribed Con Med</u>	<u>Severity</u>	<u>Continued in Trial</u>	<u>Drop Out Rate</u>
726-00-006	Neuropathic pain event in screening	Unrelated	Yes (Pregabalin)	Moderate	Yes	N/A
726-55-033	Mild pain event in screening	Unrelated	Yes (Ibuprofen)	Moderate	Yes	N/A
726-55-036	Increase pain attributed to Sana Device	Possible	No	Moderate	No	2021-02-16

726-55-051	Neuropathic pain event in screening	Unrelated	Yes (Gabapentin)	Moderate	Yes	N/A
726-55-052	Dizziness and lightheadedness	Unrelated	No	Mild	No	2021-06-01
726-55-059	Increase in pain	Unrelated	Unknown	Moderate	No	2021-07-01
726-55-070	Headache	Probable	Unknown	Mild	No	2021-12-02

Table 8: Treatment Emergent Adverse Events

<u>Subject ID</u>	<u>AE</u>	<u>Relatedness</u>	<u>Prescribed Con Med</u>	<u>Severity</u>	<u>Continued in Trial</u>	<u>Drop Out Rate</u>
726-55-036	Increase pain attributed to Sana Device	Possible	No	Moderate	No	2021-02-16
726-55-070	Headache	Probable	Unknown	Mild	No	2021-12-02

Pediatric Extrapolation

The Sana Device is indicated for patients aged 18 and older. For medical devices, the FD&C Act defines pediatric patients as persons aged 21 or younger. In this De Novo request, clinical data from patients aged 18 and older were used to support the use of the device in adult patients. It is appropriate to indicate the device for individuals 18 and older because patients aged 18 to 21 do not carry additional differences or risks relative to the adult patient population studied, and this device has a likely benefit for this group.

LABELING

The labeling (Instructions for Use) meets the requirements of 21 CFR Part 801.109 for prescription devices.

The labeling provides information to users describing the clinical data showing the safety and effectiveness of the Sana Device in the intended patient population. It also includes instructions for operating the device. Appropriate contraindications, warnings, and precautions are included to avoid hazardous situations and ensure safe use of the device as intended.

The labeling also outlines appropriate cleaning methods for home use.

RISKS TO HEALTH

The risks associated with the Sana Device are thermal injury or electrical shock, adverse tissue reaction, device failure due to interference with other devices, delayed or ineffective treatment

due to use error, headache/migraine, light and/or sound sensitivity, pain, photosensitivity, nausea, insomnia, and anxiety. The severity and incidence of these risks to health are low as demonstrated in the clinical study and non-clinical performance testing. As such, general controls are sufficient to provide reasonable assurance of safety and effectiveness. General controls include, and are not limited to, quality system regulation, including design controls (21 CFR 820) due to the inclusion of software; general labeling requirements (21 CFR 801); and medical device reporting (21 CFR 803).

Section 510(l) of the FD&C Act (21 U.S.C. 360(l)) provides that a class I device is not subject to the premarket notification requirements under section 510(k) of the FD&C Act unless the device is of substantial importance in preventing impairment of human health or presents a potential unreasonable risk of illness or injury. FDA has determined that the device does meet these criteria and, therefore, premarket notification is not required for the device, subject to the limitations of exemption in 21 CFR 890.9. Examples exceeding the limitations of exemption could include:

- Indications for non-temporary pain relief, relief of pain due to migraines, stand-alone use (i.e., use by itself, and not in conjunction with other modes of therapy), or over-the-counter use.
- The device exceeds audio stimulation of 60 dB, the device exceeds visual stimulation of 35 lux, or the device is intended to provide light stimulation while the eyes are open.
- Intended for use in populations with light and/or sound sensitivities.
- Intended for use in populations with vision and/or hearing impairments.

BENEFIT-RISK DETERMINATION

The probable risks of the device are based on the non-clinical data and the data collected in the clinical study described above. The study identified adverse events such as increased pain (1 instance) and headache/migraine (1 instance). Other probable risks resulting from device use include dizziness and lightheadedness, photosensitivity, nausea, insomnia, and anxiety. The device exhibited an acceptable safety profile in the clinical study, and any adverse events that occurred were minor and resolved without long-term sequelae. No device-related serious adverse events were observed. The results of the nonclinical testing demonstrated that the device performed as per specifications and the results did not raise concerns regarding risks to the patients.

The probable benefits of the device are also based on data collected in the clinical study as described above. There is evidence of a clinically meaningful and statistically significant improvement in neuropathic pain based on the NPSI total score results at Week 14 compared to baseline. Patients in the active group experienced an 8.75-point reduction in NPSI total score compared to sham, which is a clinically meaningful and statistically significant difference. When looking at within group differences, the active group experienced an 11.7-point improvement at Week 14 compared to baseline, which is also clinically meaningful and statistically significant.

Therefore, the clinical study demonstrates a greater improvement in neuropathic pain in the Sana Device treatment group compared to the sham group.

Sources of uncertainty in the benefits include the parallel reduction in NPSI total scores between the active and sham groups from Week 2 through Week 10. As explained above, this was due to the design of the sham device, which was intended to maintain blinding and percent dropout due to ineffective treatment. While the 4-week follow-up period mitigates some of this uncertainty by demonstrating the continued treatment effect of the active device, it is still possible the placebo effect may have impacted these results. This was considered in the benefit-risk determination. The baseline NPSI total score was unequal between groups which raised uncertainty. However, this difference was not statistically or clinically significant, and sensitivity analyses showed that it was unlikely to have an impact on the results. The use of concomitant medication was addressed by specifying the Sana Device is intended for adjunctive use. Additionally, since the Sana Device is intended for the temporary relief of neuropathic pain, the lack of longer-term follow-up data does not raise uncertainty. The dropout rate (i.e., 8 patients of 75 total) and device adherence rates (i.e., ~70%) could have contributed to the amount of missing data, which was considered in the benefit-risk determination. The sample size for the per-protocol group was also not statistically designed to evaluate differences in the outcomes based on the etiology of neuropathic pain. Lastly, the lack of blinding assessment introduced uncertainty, which was mitigated by the similar rate of dropouts per group. Additionally, the parallel improvement between active and sham groups during the treatment phase (Week 2 through Week 10) does not support that unblinding occurred because the sham group would be expected to perform significantly worse compared to active with knowledge of group assignment.

Patient Perspectives

The primary and secondary outcome measures in the clinical study were collected using patient reported outcomes. The primary outcome measure was the Neuropathic Pain Symptom Inventory (NPSI) total score, which is a patient reported pain measurement.

Patient reported secondary outcomes included: Generalized Anxiety Disorder-7 (GAD-7), Patient Health Questionnaire-9 (PHQ-9), Pittsburgh Sleep Quality Index (PSQI), and Patient Global Impression of Change Quality of Life (PGIC-QOL).

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

The Sana Device is indicated for patients aged 18 and older as an adjunct to other modes of therapy for temporary relief of neuropathic pain for use at home or in the clinic.

The probable benefits outweigh the probable risks for the Sana Device. The device provides benefits and the risks can be mitigated by the use of general controls.

CONCLUSION

The De Novo request for the Sana Device is granted and the device is classified as follows:

Product Code: QYN

Device Type: Audio-visual stimulator for pain relief

Regulation Number: 21 CFR 890.5775

Class: I