SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Stimulator, Spinal-Cord, Totally Implanted for Pain Relief

Device Trade Name: Senza® Spinal Cord Stimulation (SCS) System

Device Procode: LGW

Applicant's Name and Address: Nevro Corp.
1800 Bridge Parkway
Redwood City, CA 94065

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P130022

Date of FDA Notice of Approval: January 18, 2022

The original PMA P130022 was approved on May 08, 2015, and is indicated as an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain, and leg pain. The SSED to support the indication is available on the CDRH website (https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130022B.pdf) and is incorporated by reference here. The current supplement was submitted to expand the indication for Senza® Spinal Cord Stimulation (SCS) System

II. INDICATIONS FOR USE

The Senza®, Senza II™ and Senza Omnia™ neuromodulation systems are indicated as aids in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain, and leg pain.

The Senza®, Senza II™ and Senza Omnia™ neuromodulation systems, when programmed to include a frequency of 10 kHz, are indicated as aids in the management of non-surgical refractory back pain (intractable back pain without prior surgery and not a candidate for back surgery).

III. CONTRAINDICATIONS

The Senza, Senza II, and Senza Omnia Systems should not be used for those patients who:

- Patients who are poor SCS surgical candidates based on presentation and underlying pathology.
- Fail to receive effective pain relief during trial stimulation.
- Are unable to operate the SCS system.

IV. WARNINGS AND PRECAUTIONS

Warnings and Precautions can be found in the Physician Implant Manual, the Clinician Programmer Manual and the Patient Manual.

V. DEVICE DESCRIPTION

The Senza® Spinal Cord Stimulation (SCS) System (includes Senza, Senza II and Senza Omnia) is a neuromodulation device designed to deliver electrical stimulation for the treatment of chronic pain. The Senza System is totally implantable and delivers stimulation using implantable leads and a rechargeable, implantable pulse generator (IPG). The Senza System is implanted using a minimally invasive surgical procedure that is reversible. The IPG is implanted in a subcutaneous pocket and is capable of stimulating the spinal cord nerves when used with one or more leads. The IPG is controlled by a Patient Remote and/or the Clinician Programmer. Other components of the Senza System include an external Trial Stimulator capable of delivering the same stimulation as the IPG, Lead Extensions, Adaptors, Charger and charging system, operating room (OR) cables and surgical accessories. The Senza SCS System is shown in Figure 1 below:

Figure 1: Senza SCS System: Left to right: IPG1500, IPG2000 and IPG2500

Senza System Details – Major Components

- Implantable Pulse Generator Models: The Implantable Pulse Generator (IPG) is a rechargeable implantable device with 16 output channels capable of stimulating the spinal cord nerves through electrode leads. The IPG is designed to produce current-regulated, charge-balanced, biphasic, capacitively-coupled, rectangular output pulses. The IPG header contains the charging coil and two ports to allow the insertion of leads. The rechargeable battery is contained in a hermetically sealed housing, which is inside the hermetic IPG Titanium enclosure.

- Trial Stimulator: The Trial Stimulator is a battery-powered, handheld device capable of providing the same stimulation as the IPG. During the Trial Phase of SCS, the subject wears this external Trial Stimulator for a period of time to evaluate the effectiveness of the stimulation prior to receiving a permanent implant. The Trial Stimulator is connected to the subject's implanted leads by the use of OR cables.

- IPG or Trial Stimulator interface with other Senza components: The Charger transmits energy transcutaneously to recharge the IPG battery. The IPG and Trial Stimulator communicate with the Patient Remote or Clinician Programmer via the Programmer Wand. Patients are also able to send commands to the IPG or Trial Stimulator directly using the Patient Remote. The IPG also includes a magnetic switch for turning the therapy off by using an external magnet.

- Patient Remote Control: The Patient Remote Control is a handheld battery- operated unit able to communicate with the IPG or Trial Stimulator. The Patient Remote includes multiple controls and indicators for the purpose communicating with these components.

- Charger: This Charger is used by the subject to transcutaneously charge the IPG battery. It is a portable device powered by a rechargeable battery and can be held in one hand.

- Programmer: The Clinician Programmer programs the IPG or Trial Stimulator via the Programmer Wand via a graphical user interface (GUI).

- Programmer Wand: The Programmer Wand is the Clinician Programmer interface that allows the communication with the IPG or Trial Stimulator.

- Percutaneous Leads, Lead Extensions and Lead Adaptors: The Nevro Lead is intended to be used with the IPG or Trial Stimulator for use in delivering stimulation. The Percutaneous Lead is for single use and interfaces with the IPG, Lead Extensions, OR Cable, and lead accessories.

  The M8 and S8 Lead Adaptors allow a physician to connect an implanted Medtronic or St. Jude Medical lead, respectively, with the Nevro Lead Extension or IPG. The construction of the Lead Adaptors is identical to the Lead Extension.

Senza System Details - Surgical Accessories

- Torque Wrench: The Torque Wrench is used to tighten the set screws that lock the Percutaneous Lead into the IPG, to lock the Percutaneous Lead into a Lead Extension/Adaptors, or to activate the retention mechanism on the Active Anchors.

- Lead anchors: The Lead Anchors are used to anchor the Percutaneous Lead to the fascia or supraspinous ligament.

- Insertion Needle: The Insertion Needle is used during implant surgery to introduce the Percutaneous Lead between the vertebrae into the epidural space.

- Coiled Lead Blank: The Coiled Lead Blank is optionally used during surgery to clear a path for the introduction of the Percutaneous Lead into the epidural space.

- Stylets: The Stylets are used to maneuver the Lead through the epidural space to the desired implant location.

- IPG Port Plug: The IPG Port Plug is provided to seal the port of the IPG that is not in use when only one Lead is implanted.

- OR Cables: The Operating Room (OR) Cables make electrical and mechanical connections between the Trial Stimulator and the Percutaneous Leads or Lead Extensions.

- Tunneling Tool: The Tunneling Tool creates a subcutaneous tunnel for the leads from the IPG site to the midline incision.

- IPG Template: The IPG Template acts as an optional aid for physicians in proper sizing of the IPG implant pocket.

- Mx Trial Adaptor: The Mx Trial Adaptor is intended to connect a Medtronic OR cable to the Nevro External Trial Stimulator.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of chronic intractable pain of the trunk and/or limbs. Patients are typically treated on a treatment continuum with less invasive therapies prescribed first. Established non-surgical treatment options include, but are not limited to oral medications, massage therapy, physical/occupational/exercise therapy, psychological therapies (e.g., behavior modification, hypnosis), Transcutaneous Electrical Nerve Stimulation (TENS), acupuncture, sympathetic nerve blocks, epidural blocks, intrathecal blocks, and facet joint blocks. The surgical treatment options for these patients include sympathectomy, implantable intrathecal drug delivery systems, partially implanted SCS systems (power source is external) and commercially available fully implantable SCS systems. Each alternative has its own advantages and disadvantages. A

patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Senza System has been in commercial distribution in the U.S, European Union (EU) and Australia for several years. Regulatory agency marketing approvals were received for the Senza System in May 2010 for the EU, June 2011 for Australia and May 2015 for the US. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of potential adverse effects (e.g., complications) associated with the use of SCS systems. The adverse effects include: (1) those associated with any surgical procedure, (2) those associated with the SCS system placement procedures, and (3) those associated with having an implanted SCS system to treat pain, including the Senza SCS System. In addition to the risks listed below, there is the risk that the SCS therapy may not be effective in relieving symptoms, or may cause worsening of symptoms. Additional intervention may be required to correct some of the adverse effects.

Risks associated with Implant Procedures

- Risks associated with anesthesia, including cardiac arrest
- Surgical complications, such as infection, cellulitis, abscess, fever, sepsis, bleeding
- Cerebrospinal fluid leak
- Intracranial hypotension
- Hematoma, seroma or thrombosis
- Epidural hemorrhage
- Impaired or inadequate wound healing, wound dehiscence
- Temporary or persistent tenderness or pain at implant site
- Lead migration leading to ineffective pain control or other undesirable changes in stimulation
- Suboptimal lead or IPG placement or migration requiring revision or explant
- Spinal cord compression; nerve, nerve root, or spinal cord injury
- Weakness, lack of coordination, or numbness
- Paralysis
- Death

Risks associated with SCS Stimulation

- Loss of pain relief, loss of paresthesia, unpleasant paresthesia
- Increased pain
- Undesirable stimulation due to cellular changes over time in tissue around electrodes, changes in electrode position, loose electrical connections, or lead failure
- Uncomfortable stimulation of tissue around the leads including skin and muscle

- Other undesirable sensation such as tingling or prickling

Risks associated with Implanted Device Components

- Tissue reaction or allergy to implanted materials
- Persistent pain at implant site (lead or IPG)
- Failure of device components or the battery including lead breakage or movement (migration), hardware malfunctions, loose connections, electrical shorts or open circuits, and lead insulation breaches
- Failure or malfunction resulting in ineffective pain control or other undesirable changes in stimulation, and possibly requiring explant and re-implantation
- Skin erosion or seroma at the lead or IPG site
- Pressure sores
- External sources of electromagnetic interference that cause the device to malfunction and could affect stimulation
- Exposure to magnetic resonance imaging (MRI) can result in heating of tissue, image artifacts, induced voltages in the IPG and/or leads, and lead dislodgement

Risk associated with External Device Components

- Tissue reaction or allergy to external materials
- Uncomfortable heating effects, discomfort or burn

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

IX. SUMMARY OF NONCLINICAL STUDIES

Pre-clinical studies (bench and animal) previously submitted to FDA in the Original PMA application (P30022) and supplements continue to support the safety of the commercially available The Senza SCS System for treatment of chronic intractable pain of the trunk and/or limbs. No additional preclinical studies were required to evaluate the safety of The Senza SCS therapy for the treatment of the new patient populations. The previously approved supplements which support the device and its components are listed below in **Table 1.**

Table 1: Summary of Senza SCS system Approvals

System/Device Copoment	Approval Reference
Approval for 0.016” curved stylet with 22 degree bend angle	P130022/S041
Approval for MR Conditional labeling for the Surpass-C surgical leads used with the Senza Spinal Cord Stimulation System	P130022/S040
Labeling expansion claim to include Painful Diabetic Neuropathy (PDN)	P130022/S039
Approval for software and firmware updates to Senza components	P130022/S038

Approval for Oscor, a second source for percutaneous lead manufacturing	P130022/S037
Approval for the Senza Bluetooth Trial system including the next generation Trial stimulator, a compatible Bluetooth Trial Patient remote and a software update to the clinician programmer to configure the Bluetooth Trial Stimulator.	P130022/S036
Transfer of FDA approved Nordson facility from Sunnyvale to San Jose for manufacturing Implantable Pulse generators	P130022/S035
Addition of a second Cirtec site in Costa Rica for percutaneous lead production	P130022/S034
Approval for adding B1+RMS scanner limits to support 1.5T Full Body MRI conditional labeling for IPG1000/1500/2000/2500 with Surpass surgical and Percutaneous leads to enhance the safety of the Senza SCS system.	P130022/S033
Approval for additional lead sizes and configurations designated as Surpass-C Surgical Leads.	P130022/S031
Change in manufacturing site for IPG header component	P130022/S029
Approval for use of alternate proposed Integer battery (M3580) on Senza Implantable Pulse Generator, model IPG2000 (Senza II) of Nevro's Senza Spinal Cord Stimulator (SCS) System and associated firmware updates.	P130022/S028
Approval for mechanical and design changes made to the current charger (CGR1000) for the Senza Spinal Cord Stimulation (SCS) system to improve cosmetics and reduce the size of the charger. The modified patient remote charger will now be offered as model CGR2500.	P130022/S027
Approval to make changes to the software for the Clinical Programmer, model CLPG2000/CLPG2500 upgrading the software from version 1.7 to 2.0.	P130022/S026
Approval for a change in the approved packaging for the IPG (NIPG1500, NIPG2000), Lead Extension kits (MADP2008-25B M8, SADP2008-25B S8), and Lead Adapter kits (LEAD2008-25B, LEAD2008-35B, LEAD2008-60B) of your Senza Spinal Cord Stimulation (SCS) System.	P130022/S025
Approval for a new optional accessory tool - Nevro passing elevator accessory tool (PEAT) for use with Nevro Senza Spinal Cord Stimulation (SCS) System.	P130022/S024
Approval to modify the patient remote cosmetically and to reduce the size; update the patient remote model numbers to PTR2300 and PTR2500; update the firmware for patient remote, model PTR2500 and the clinician programmer, model CLPG2000/CLPG2500 to support 5 stimulation therapy settings; and update the firmware to the IPG (renamed Omnia Senza IPG, Model NIPG2500) to support up to 5 stimulation settings.	P130022/S023

Approval for a manufacturing site located at Integer (dba Greatbatch Medical S. de R.L. de C.V.), Blvd. Hector Teran Teran No. 20120, Ciudad Industrial Tijuana, Baja California, Mexico 22444 for the manufacturing of implantable pulse generators for the Senza Spinal Cord Stimulation (SCS) System.	P130022/S022
Approval for changes made to MRI Guidelines Manual for the Senza System by adding a new MRI claim for IPG1000/1500/2000.	P130022/S021
Approval for conditional Magnetic Resonance labeling for the Senza Implantable Pulse Generator (IPG) model IPG2000.	P130022/S019
Approval for changing the length and shape of the handle, and the method of securing the cap and wire to the handle of the Stylets distributed with the Senza Spinal Cord Stimulation System	P130022/S018
Approval for a manufacturing site located at Pro-Tech Design & Mfg, Inc., 13719 Borate St, Sante Fe Springs, CA	P130022/S017
Alternate supplier of the Litz Wire used for manufacturing the Senza SCS System Charger sub-assembly	P130022/S016
Second contract manufacturer (Sparton) to conduct manufacturing activities for one of Senza SCS System's components (i.e., Trial Stimulator)	P130022/S015
Approval for Magnetic Resonance (MR) conditional labeling changes	P130022/S014
Approvals for changes made for the Senza Implantable Pulse Generator, IPG2000	P130022/S013
Implement manufacturing process changes to allow for the use of virtual machine software (VMware) to provide an isolated and safe environment from which to run the FDA approved PG2000 Clinician Programmer software v1.7	P130022/S012
Packaging configuration change (i.e., pre-loaded percutaneous lead with the 0.014" curved stylet) to the Senza SCS System	P130022/S011
Approval for a manufacturing site located at Pro-Tech, 4041 Express Street, Arlington, Texas for kitting of components in cleanrooms, final packaging including labeling and visual inspection of the final product prior to shipment for sterilization.	P130022/S010
Approval for a design change for the Surpass Surgical Lead to remove the marker band and change the color of one lead leg	P130022/S009
Approval for software changes to the Clinician Programmer Model PG2000	P130022/S008

Approval to use a larger volume of sterilization load (from 4 pallets to 10 pallets) for the ethylene oxide (EO) sterilization of Senza SCS System products	P130022/S007
Process changes to the battery charger, including the addition of an adhesive to a component on the printed circuit board (PCB), minor alterations to the PCB layout to improve manufacturability, and the addition of torque wrenches	P130022/S006
Approval to update the design of the charging coil to eliminate the termination wraps at the end of the charging coil	P130022/S005
Approval for Surgical Lead Models LEAD3005-xx, LEAD3015-xx, and LEAD3025-xx	P130022/S004
Approval for minor changes in the Senza SCS System Implantable Pulse Generator (IPG) and trial simulation (TSM) firmware	P130022/S002
Modification in the manufacturing process of the Connector stack sub- assembly	P130022/S001
Approval for the Nevro Senza SCS System	P130022

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The Senza SCS systems are approved as an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain, and leg pain.

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness with the Senza System when programmed to include a frequency of 10kHz aids in the management of non-surgical refractory back pain (NSRBP) patients in the US. Data from this clinical study were the basis for the PMA approval decision. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were enrolled between September 5, 2018 and January 27, 2020. The database for the PMA Supplement P130022/S042 reflected data collected through April 2021 and included 211 patients. There were 15 study sites.
Senza-NSRBP was a post-market multi-center randomized controlled study where patients who met the eligibility criteria were randomized at a ratio of 1:1 to either: 1) 10kHz SCS

therapy with conventional medical management (CMM), or 2) to continue with CMM alone. Subjects had the option to crossover at 6 months. The primary endpoint was assessed at 3 months, secondary endpoints at 6 months, and observational assessments will continue until study completion. Subjects in both arms will continue with the conventional medical management they have been receiving. The choice of appropriate medical management is made by the Investigator as determined to be the best standard of care for each individual patient. The original study duration was 12 months following randomization/baseline, but a study extension allowed for an optional consent for study observation out to 24 months.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the Senza SCS System study was limited to patients who met the specified inclusion criteria. Key inclusion criteria were:

   a. Patients with chronic, refractory, primary axial back pain who based on consultation with a spine surgeon or neurosurgeon: i. Are not candidates for or are not eligible for major lumbar spine surgery (such as fusion, microdiscectomy, laminectomy, arthroplasty, etc.); or
   b. Present with spinal conditions for which surgery is typically indicated, but are not considered eligible for surgery due to lack of severity, lack of clearly identifiable structural cause, lack of desire to undergo major lumbar surgery, or other factors.
   c. Pain should have a predominant neuropathic component as per the investigator's clinical assessment
   d. Have not had any surgery for back or leg pain, or any surgery resulting in back or leg pain
   e. Considering daily activity and rest, have average back pain intensity of ≥ 5 out of 10 cm on the Visual Analog Scale (VAS) at enrollment
   f. Be 18 years of age or older at the time of enrollment

   Patients were not permitted to enroll in the Senza SCS System study if they met any of the specified exclusion criteria.

   a. Have a diagnosed back condition with inflammatory causes of back pain (e.g., ankylosing spondylitis or diseases of the viscera)
   b. Have a medical condition or pain in other area(s), not intended to be treated with SCS, that could interfere with study procedures, accurate pain reporting, and/or confound evaluation of study endpoints, as determined by the Investigator
   c. Have evidence of an active disruptive psychological or psychiatric disorder identified as the primary condition or other known condition significant enough to impact perception of pain, compliance of intervention and/or ability to evaluate treatment outcome, as determined by the investigator in consultation with a psychologist
   d. Have a current diagnosis of a progressive neurological disease, spinal cord tumor, or severe/critical spinal stenosis
   e. Have a current diagnosis of a coagulation disorder, bleeding diathesis, progressive peripheral vascular disease or uncontrolled diabetes mellitus that would add unacceptable risk to the procedure

f. Have an opioid addiction or drug seeking behavior as determined by the Investigator
g. Have an existing drug pump and/or SCS system or another active implantable device such as a pacemaker
h. Have prior experience with neuromodulation devices (SCS, Peripheral Nerve Stimulators, Dorsal Root Ganglion Stimulation (DRG), multifidus muscle stimulation)
i. Have an active systemic or local infection
j. Be pregnant (participants of child-bearing potential that are sexually active must use a reliable form of birth control).
k. Have within 6 months of enrollment a significant untreated addiction to dependency producing medications or have been a substance abuser (including alcohol and illicit drugs)

2. Follow-up Schedule

Subjects were scheduled to return for follow-up examinations at 1, 3, 6, 9, 12, 18, and 24 months in both study arms. Subjects randomized to the 10kHz SCS therapy group underwent a trial stimulation phase lasting up to 14 days with an external stimulator to determine his/her response to this therapy. At the end of the trial phase, subjects had a neurological assessment as well as an assessment for pain. Those who had a successful trial phase, defined as a 50% or greater reduction in back pain from baseline, were eligible to proceed to permanent implantation of a Senza System. At the 6-month assessment, dissatisfied subjects with insufficient pain relief and agreement of the Investigator could opt to crossover to the other study arm. Subjects who crossed over will complete the remainder of the scheduled follow-up to 12 months, with an optional extension up to 24 months. The baseline VAS, medication usage, medical history, Oswestry Disability Index (ODI), Short-Form McGill Pain Questionnaire (SF-MPQ-2), The Pain and Sleep Questionnaire three-item index (PSQ-3), EuroQol five-dimensional questionnaire (EQ-5D-5L), Physical health evaluation (SF-12), Patient Health Questionnaire, neurological assessment, 50 ft. walk test, work status, and healthcare utilization were all taken preoperatively. Post operatively, the objective parameters measured during the study included the same assessments, but also Patient Global Impression of Change (PGIC), Clinician Global Impression of Change (CGIC) and Subject Satisfaction. Adverse events and complications were recorded at all visits. The key time points up to 12 months for each assessment are shown in figure 2.

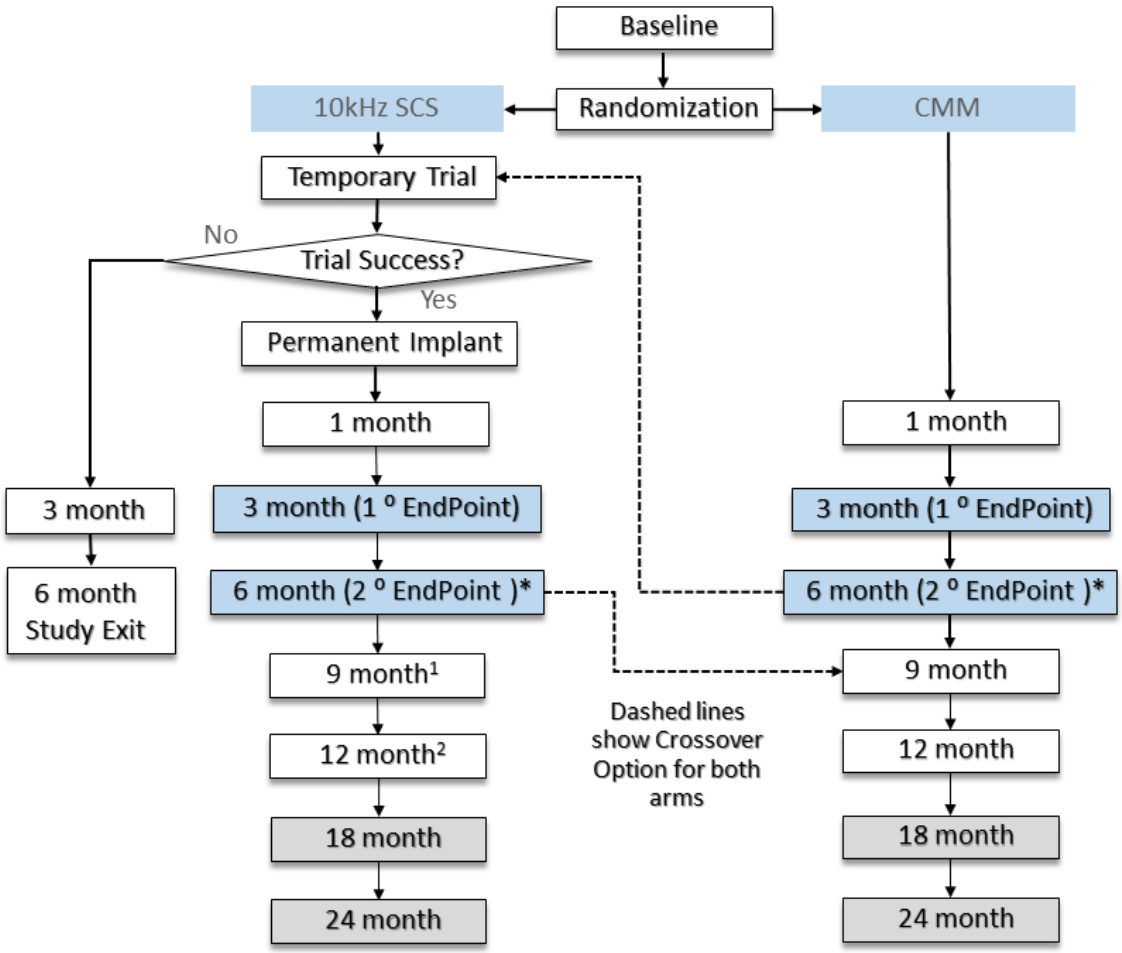

Figure 2: Study Flowchart

(†Primary endpoint analysis; *Option to cross-over to other therapy arm)

3. Clinical Endpoints

The primary endpoint of this study is a composite of safety and effectiveness, specifically the difference between treatment groups in responder rates at 3- month follow-up in subjects without a clinically meaningful neurological deficit compared with baseline. A responder is defined as a subject with ≥ 50% back pain reduction from baseline.

The effectiveness of the Senza SCS system was demonstrated by a decrease in back pain VAS by at least 50% at 3 months Post-Permanent Device Activation as compared with Baseline

The safety of the Senza SCS system was assessed by characterizing clinically meaningful deficits in neurological status (primary) and adverse events (secondary) at all study visits.

Neurologic status includes motor, sensory and reflex functions, which will be characterized as improved, maintained, or a deficit as compared with baseline status as follows:

- A clinically meaningful neurological improvement is defined as a significant persistent improvement in neurological function that impacts subject's well-being and is attributable to a neurological finding; and is new or improved as compared with the baseline assessment.
- A clinically meaningful neurological deficit is defined as a treatment-related significant persistent abnormality in neurological function that impacts subject's well-being and is attributable to a neurological finding; and is new or worsened as compared with the baseline assessment.
- If neither a clinically meaningful neurological improvement nor a clinically meaningful neurological deficit is observed, then neurologic status is maintained.

For a clinically meaningful neurological deficit from Baseline, persistent is defined as lasting beyond what would be expected for a transient event in this population and unable to be resolved through device reprogramming.

Secondary endpoints:

If the primary endpoint was found to be statistically significant at an alpha level of 0.05, then the following secondary endpoints were successively tested in a hierarchical manner in the order shown with the same two-sided alpha level of 0.05 until statistical significance cannot be demonstrated.

1. Difference between the treatment groups in proportion of subjects with a lower limb pain VAS score ≤ 3.0 cm at 3 months.
2. Difference between the treatment groups in crossover rates.
3. Difference between the treatment groups in responder rates at 6 months.
4. Difference between the treatment groups in the proportion of remitters (remission is defined as having a lower limb pain VAS score of ≤ 3.0 cm for at least 6 months) at 6 months.

5. Difference between the treatment groups in the proportion of subjects with overall improvement from baseline in neurological assessment (motor, sensory, reflex) at 3 months.
6. Difference between the treatment groups in the proportion of subjects with overall improvement from baseline in neurological assessment (motor, sensory, reflex) at 6 months.
7. Difference between the treatment groups in changes in health-related quality of life as assessed by the EuroQol Five Dimensions questionnaire (EQ-5D-5L) at 6 months.
8. Difference between the treatment groups in the average percentage change from baseline in HbA1c levels at 6 months.

B. Accountability of PMA Cohort

A total of 211 subjects were enrolled in this study at 15 US clinical sites. A total of 159 subjects were randomized, 83 in 10kHz SCS group and 76 in the CMM alone group. These 159 subjects comprise the ITT analysis population. With 68 of the 10kHz SCS subjects and 75 of the CMM subjects completing 3-Month Primary Endpoint Assessment, a total of 145 subjects were included in the PP analysis population.

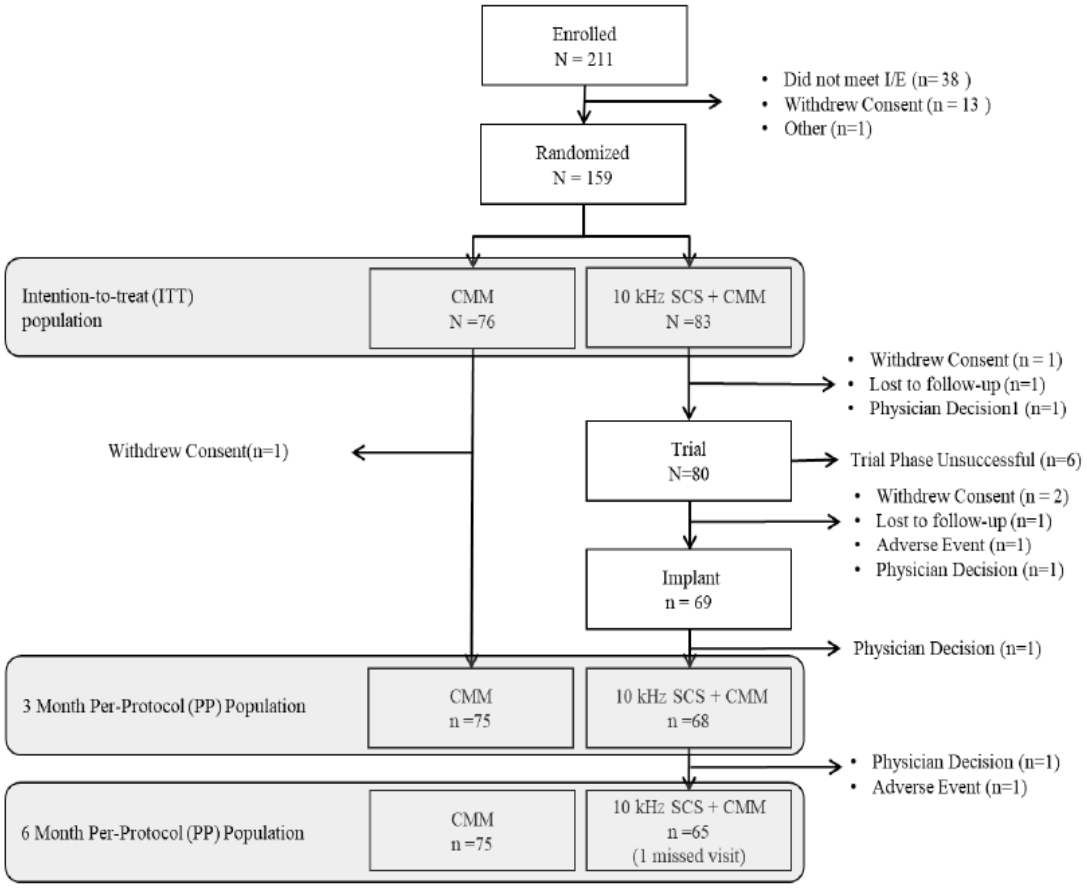

Figure 3: Number of Subjects in the Study by Phase

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pain study performed in the US. See **Table 2** below.

Table 2: Study Demographics and Baseline Characteristics

	10kHz SCS (n=83)	**CMM (N=76)**
Age in years, median (range)	53.0 (29.0 to 87.0)	58.5 (26.0 to 77.0)

Sex (female). n (%)	50 (60.2%)	40 (52.6%)
Race, n (%)[1]		
	10kHz SCS (n=83)	**CMM (N=76)**
White	75 (90.4%)	73 (96.1%)
Black of African American	4 (4.8%)	2 (2.6%)
American Indian or Alaska Native	2 (2.4%)	1 (1.3%)
Asian	2 (2.4%)	0 (0.0%)
Native Hawaiian or other Pacific Islander	1 (1.2%)	0 (0.0%)
Other	1 (1.2%)	0 (0.0%)
Years since diagnosis of Chronic low back pain (CLBP), median (range)	8.5 (0.0 to 52.0)	8.0 (1.0 to 59.0)
Back Pain VAS (cm)		
Mean (SD)	7.4 (1.2)	7.2 (1.0)
Median, Range	7.6 (4.0 to 10.0)	7.2 (4.5 to 9.9)
Baseline Leg Pain Present, n (%)[2]	52 (62.7%)	45 (59.2%)
Pain Etiology[1], n (%)		
Degenerative disc disease	60 (72.3%)	52 (68.4%)
Internal disc disruption/annular tear	8 (9.6%)	6 (7.9%)
Spondylosis	55 (66.3%)	49 (64.5%)
Lumbar facet-mediated pain	24 (28.9%)	25 (32.9%)
Radiculopathy	34 (41.0%)	35 (46.1%)
Mild/mod spinal stenosis	23 (27.7%)	24 (31.6%)
Spondylolisthesis	7 (8.4%)	9 (11.8%)
Sacroiliac dysfunction	3 (3.6%)	5 (6.6%)
Total Pain Detect Scores		
Mean (SD)	17.8 (6.9)	17.2 (7.4)
Median (Range)	18.0 (1.0 to 33.0)	17.5 (0.0 to 37.0)
Non-Surgical Candidate reason, n (%)		
• Patient is not a good surgical candidate based on presentation of underlying pathology	65 (78.3%)	61 (80.3%)
• Patient is a candidate for surgery but declines	11 (13.3%)	10 (13.2%)

• Patient not recommended due to moderate to high surgical risk due to comorbidities or other clinical conditions (smoker; obese; CHF)	6 (7.2%)	5 (6.6%)
Subjects on Opioids at Baseline[3], n (%)	33 (39.8%)	35 (46.1%)

[1]Subject may have more than one race or etiology
[2]Subjects with a left or right lower limb baseline pain score greater or equal to 6 are included only
[3]With complete opioid diary assessment

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the ITT population of 159 patients available that were randomized. The safety population includes all subjects randomized, with the three subjects randomized to 10kHz SCS who withdrew prior to trial being analyzed as CMM. Overall, 69 study subjects had a total of 33.3 implant years as of the 6-month follow-up. The key safety outcomes and adverse events for this study are presented below in Table 3 to Table 5.

Table 3: Summary of Adverse Events

	CMM Alone (N=79)		**10kHz SCS (N=80)**	
	Number of AEs	**Number (%) of Subjects with AE**	**Number of AEs**	**Number (%) of Subjects with AE**
All AEs	**11**	**5 (6.3%)**	**29**	**25 (31.3)**
Serious AEs	10	4 (5.1%)	6	6 (7.5%)
Study-related serious AEs	0	0	4	4 (5.0%)
Non-serious AEs	1	1 (1.3%)	23	20 (25.0%)
Study-related non- serious AEs	1	1 (1.3%)	23	20 (25.0%)

UADEs	0	0 (0.0%)	0	0 (0.0%)

Table 4: Summary of Adverse Events

	CMM alone (N=79)		10kHz SCS (N=80)	
	Number of AEs	**Number (%) of Subjects with AE**	**Number of AEs**	**Number (%) of Subjects with AE**
All AEs	**11**	**5 (6.3%)**	**29**	**25 (31.3%)**
AEs by relationship to study				
Not related	10	3 (3.8%)	2	2 (2.5%)
Related	1	1 (1.3%)	27	23 (28.8%)
Device related	0	0 (0.0%)	10	10 (12.5%)
Procedure related	0	0 (0.0%)	11	10 (12.5%)
Stimulation / Therapy	0	0 (0.0%)	4	4 (5.0%)
CMM-related	1	1 (1.3%)	2	2 (2.5%)
AEs by phase at onset				
Between Consent and Randomization	1	1 (1.3%)	0	0 (0.0%)
Trial Phase			5	5 (6.3%)
Between Trial Phase and Permanent Phase			3	3 (3.8%)
Permanent Implant-Month 3 (10KHZ SCS) or Randomization-Month 3 (CMM)	6	4 (5.0%)	18	17 (21.3%)
Month 3-6	4	3 (3.8%)	3	3 (3.8%)
AEs by severity				
Mild	0	0 (0.0%)	10	10 (12.5%)
Moderate	4	2 (2.5%)	12	10 (12.5%)
Severe	7	3 (3.8%)	7	6 (7.5%)

AEs by outcome				
Resolved	11	5 (6.3%)	28	23 (83.8%)
Ongoing	0	0 (0.0%)	1[a]	1 (1.3%)
	CMM alone (N=79)		**10kHz SCS (N=80)**	
	Number of AEs	**Number (%) of Subjects with AE**	**Number of AEs**	**Number (%) of Subjects with AE**
Unknown	0	0 (0.0%)	0	0 (0.0%)

[a] One ongoing AE related to IPG pocket intermittent pain

Table 5: Study-Related Adverse Events Description

Preferred Term	CMM alone (N=79)		10kHz SCS (N=80)	
	Number of AEs	**Number (%) of Subjects with AE**	**Number of AEs**	**Number (%) of Subjects with AE**
Total # of Study Related AEs	**1**	**1 (1.3%)**	**27**	**23 (28.8%)**
Device Related AEs	0	0	10	10 (12.5%)
Implant Site Pain	0	0	5	5 (6.3%)
Lead dislodgement	0	0	2	2 (2.5%)
Back Pain	0	0	1	1 (1.3%)
Implant Site Infection	0	0	1	1 (1.3%)
Device Site Discomfort	0	0	1	1 (1.3%)
Procedure Related AEs	0	0	11	10 (12.5%)
Implant Site Infection	0	0	1	1(1.3%)

Cerebrospinal Fluid Leakage	0	0	2	2 (2.5%)
Incision Site Pain	0	0	1	1 (1.3%)
Cellulitis	0	0	1	1 (1.3%)
Impaired Healing	0	0	1	1 (1.3%)
Incision Site Erythema	0	0	1	1 (1.3%)
Medical Device Site Haemorrhage	0	0	1	1 (1.3%)
Muscle Spasms	0	0	1	1 (1.3%)
Osteomyelitis	0	0	1	1 (1.3%)
Pyrexia	0	0	1	1 (1.3%)
Stimulation Related AEs	0	0	4	4 (5.0%)
Therapeutic Product Ineffective	0	0	2	2 (2.5%)

Preferred Term	**CMM alone (N=79)**		**10kHz SCS (N=80)**	
	Number of AEs	**Number (%) of Subjects with AE**	**Number of AEs**	**Number (%) of Subjects with AE**
Back Pain	0	0	1	1 (1.3%)
Device Stimulation Issue	0	0	1	1 (1.3%)
CMM Related AEs	1	1 (1.3%)	2	2 (2.5%)
Adverse Drug Reaction	1	1 (1.3%)	0	0 (0.0%)
Fatigue	0	0 (0.0%)	1	1 (1.3%)
Lethargy	0	0 (0.0%)	1	1 (1.3%)

Safety Conclusions: Overall, the results support the safety of the Senza System for treatment of the NSRBP patient population. As such, the results of this study provide a reasonable assurance that Senza System is safe, as defined by 21 CFR 860.7(d) (1). The study demonstrates that the probable benefits to health from use of the Senza System for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risk.

2. Effectiveness Results

Primary endpoint:
There was a total of 76 subjects randomized to CMM alone and 83 subjects randomized to 10kHz SCS, for a total of 159. Six subjects randomized to 10kHz SCS had failures in the trial phase and were included in the ITT analysis.

There were 10 subjects with missing 3-month assessments, 1 CMM Alone, and 9 10kHz SCS. In a worst-case imputation, if the 1 missing subject randomized to CMM Alone was considered a responder and the 9 missing subjects randomized to 10kHz SCS were all considered non-responders, the comparison would be responder rates of 66.3% (55/83) in the 10kHz arm versus 2.6% (2/76) in the CMM arm at 3 months, with an associated p-value < 0.001.
Considering an ITT with Known Status population, 1.3% (1/75) of CMM subjects met the primary endpoint compared to 74.3% (55/74) of 10kHz SCS subjects ($p < 0.001$) at 3 months. This analysis includes the 10kHz SCS trial phase failures (n=6) as non-responders for the primary endpoint.

The per-protocol population for the primary endpoint includes all subjects randomized to CMM Alone with a 3 Month primary endpoint assessment and all subjects randomized to 10kHz SCS who received a permanent implant and had a 3 Month primary assessment, resulting in 1.3% (1/75) of CMM subjects who met the primary endpoint compared to 80.9% (55/68) of 10kHz SCS subjects who met the primary endpoint ($p < 0.001$).

Secondary endpoints:
After the study primary endpoint was found to be statistically significant with a two-sided alpha of 0.05, pre-specified secondary endpoints were tested for significance in a hierarchical fashion with the same two-sided alpha of 0.05 until statistical significance could not be demonstrated. Secondary endpoints were evaluated in the PP population at 6 months in the order listed below (1-5).

1) The proportion of subjects in the 10kHz SCS arm who achieved a decrease of at least 10 pts in ODI score was significantly higher than the CMM arm, 78.5% vs 4.0% for respectively (difference = 73.1, $p < 0.001$).
2) A significantly greater percent change in back pain for the 10kHz SCS group was reported with an average 72.0% reduction versus an average 6.2% increase in pain for the CMM group. (difference = 78.2%, $p < 0.001$).
3) The proportion of patients reporting "Better" to a "A Great Deal Better" on PGIC was 70.8% and 1.3% for the 10kHz SCS arm and CMM arm respectively, (difference of 69.4%, $p <0.001$).
4) The change in the EQ-5D-5L Index Score was compared between groups, with 10kHz SCS group achieving 0.20 vs 0.04 for the CMM group (difference = 0.24, $p <0.001$).
5) The average change in opioid daily dose in milligram morphine equivalents (MME) was compared between groups including all subjects on opioids at baseline or at least one follow-up. There was a significant reduction in opioid daily dose in the 10kHz SCS group versus no significant change in the CMM group (-17.7 vs 1.1 MME per day respectively, $p < 0.001$)

Effectiveness Conclusions:
The results of this study provide a reasonable assurance that the Senza System is effective, as defined by 21 CFR 860.7(e) (1). The study demonstrated clinically significant results in a significant portion of the target population for its intended uses and conditions of use, when accompanied by adequate directions for use.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient populat

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The clinical study included 18 investigators of which none were full-time or part-time employees of the sponsor and four investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none

Significant payment of other sorts: five investigators

Proprietary interest in the product tested held by the investigator: none

Significant equity interest held by investigator in sponsor of covered study: none

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

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The sponsor provided data from a prospective, multicenter, randomized controlled trial (Senza-NSRBP) which comprised of 159 subjects in the ITT population and 143 subjects in the PP population. This included 76 subjects in the CMM alone group and 83 subjects in the 10kHz SCS group.

These patients typically have impaired quality of life including sleep disturbance to increased nighttime pain, reduced function and intolerable medication side-effects.
The primary objective of this study was to obtain evidence of safety and effectiveness of the Senza System for the treatment of a subset of the approved population who exhibit intractable pain in the back but are not suitable for surgery and have not had previous back surgery.

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

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

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

All primary and secondary endpoints were met, verifying that adding 10kHz SCS to CMM results in significant improvement in pain relief, function, quality of life, awareness of positive change, as well as reduction in daily opioid use. It is significant that 80.0% of the group receiving 10 kHz therapy achieved greater than 50% pain relief at 3 and 6 months post-implant, particularly given the refractoriness of the population and the length of time diagnosed with chronic back pain. In addition to pain relief, the secondary outcome measures demonstrated improvement in other indirect measures of pain. The average increase in function seen in the 10 kHz SCS arm was several times the clinically significant threshold. Function is an important measure of therapy efficacy and increased ability to do daily tasks because of reduced pain impacts a patient's quality of life including their ability to work and reducing the need for caretakers.

The positive outcomes for the 10kHz SCS arm were stable at 3 and 6 months, indicating sustained therapy durability.

The 10 kHz SCS arm reduced their daily opioid dose by 39.0% on average, with 27.3% able to stop using opioids all together by six months. Reduction in opioid use has a positive economic impact in terms or prescription payments, as well as on health care utilization related to lower adverse side effects and lower risk of overdose. Reflecting these other outcomes, the overall quality of life improvement as measured by EQ5D5L was greater than two times the published minimum clinically important difference in the 10kHz SCS arm.

B. Safety Conclusions

The risks of the device are based on the data collected in a clinical study conducted to support PMA approval as described above. There were no stimulation-related neurological deficits reported in the study.

The risks of the device are based on nonclinical laboratory and animal studies, historical SCS literature, data collected in the pivotal Senza randomized controlled trial (RCT), extensive post-market data, published commercial data reviews, as well as the Senza-NSRBP study presented here, conducted to support PMA approval as described above.

The Senza System is being used in this study for an on-label, chronic low back pain indication, but with the added criteria of no previous spine surgery, and a surgery consult to determine that subjects are not a candidate for surgery. The implant of the IPG and leads was per standard of care as specified in the physician's manual. The study population was essentially equivalent in demographics to the commercially treated population. One exception to this was the required surgeon consult, which was needed to ensure the study population were not surgical candidates.

The study related AE reported rates (22 subjects experienced study related AE or 27.5% of the 10kHz SCS safety population) is similar to the study-related AE rate of 27.7% reported from the Senza-RCT which supported PMA P130022. The study related SAEs include four SAEs reported in 4 (5.0%) 10kHz SCS subjects, all procedure related and resolved without sequelae. Neither of the SAEs were categorized as both unanticipated and device-related; thus, they were not considered as an unanticipated adverse event (UADE).

There were 2 explanted (2.9% of the 69 who received permanent implant) due to wound complications. Zero explants due to loss of efficacy.

Overall, the results support the safety of the Senza System for treatment of the NSRBP patient population. As such, the results of this study provide a reasonable assurance that Senza System is safe, as defined by 21 CFR 860.7(d) (1).

C. Benefit-Risk Determination

Non-surgical refractory back pain (NSRBP) patients do not achieve satisfactory pain relief with conventional medical management, and do not have a pathology that is amenable to surgery, therefore there is a need for additional treatment options. Most clinical evidence for SCS efficacy is for treatment of chronic spinal pain after surgery, commonly termed failed back surgery syndrome (FBSS) with only a few studies reporting outcomes in those who have not had spine surgery. This study provides important level 1 evidence on the clinical efficacy and cost effectiveness of 10kHz SCS SCS in this patient group, in order to support clinical decision making.

The probable benefits of the device are based on data collected in this clinical study conducted to support PMA approval as described above. The primary endpoint was the comparison of the proportion of subjects who were responders in each arm at 3 months, with a responder defined as at least 50% pain relief. The primary endpoint was met ($p < 0.001$), demonstrating the efficacy of the 10 kHz SCS therapy (74.3% and 80.9% responder rate for ITT and PP analysis respectively), and confirming the refractoriness

of the CMM arm which only obtained a 1.3% responder rate. The secondary endpoints were evaluated at 6 months and were meant to compare clinical outcomes in terms of other important dimensions, including function, global impression of change, health related quality of life, and reduction in daily opioid dose. All of the five secondary endpoints showed a significantly superior outcome for the 10 kHz SCS group.

The probable risks of the device are also based on data collected in this clinical study conducted to support PMA approval as described above. The results of the Senza-NSRBP study, along with the pivotal Senza-RCT support the safety of the Senza therapy. The adverse events that were reported were consistent with the safety profile of SCS systems including what was reported for the Senza-RCT. Rates of study related AEs and SAEs reported in this study are consistent with adverse events reported in Senza-RCT and are anticipated of this device type. There are no new risks or new adverse events identified in this subset of the patient population.

Patient Perspective

This submission did not include specific information on patient perspectives for this device.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use, in the NSRBP population, which is a subset of the population included in the pivotal Senza-RCT. The results from this Senza-NSRBP study combined with the pivotal Senza-RCT support a reasonable assurance of the safety and efficacy of the Nevro SCS System, as well its long-term performance, when used in a manner consistent with its labeling and intended use. The analyses also support a clinical benefit to risk determination that is overall favorable to this NSRBP patient population.

The evidence supporting the safety and effectiveness of the Nevro SCS System is based from a post- market clinical study. The analyses also support a clinical benefit to risk determination that is overall favorable to this patient population.

XIV. CDRH DECISION

CDRH issued an approval order on January 18, 2022

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.