DE NOVO CLASSIFICATION REQUEST FOR NEUROLYSER XR

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **High intensity focused ultrasound system for peripheral neural tissue ablation.** A high intensity focused ultrasound system for peripheral neural tissue ablation is a device that transmits ultrasound energy to produce thermal lesions in a defined, targeted volume of peripheral nervous tissue through acoustic coupling.

NEW REGULATION NUMBER: 21 CFR 882.4420

CLASSIFICATION: Class II

PRODUCT CODE: SGN

BACKGROUND

DEVICE NAME: Neurolyser XR

SUBMISSION NUMBER: DEN250015

DATE DE NOVO RECEIVED: April 24, 2025

CONTACT: FUSMobile, Inc.
6120 Windward Parkway, Suite 210
Alpharetta, Georgia 30005

INDICATIONS FOR USE

The Neurolyser XR is indicated for the thermal ablation (neurolysis) of the medial branch nerve of the lumbar facet joint(s) (L1 to L5) for the treatment of chronic, facet-mediated low back pain of at least 6 months duration and a confirmed diagnosis based on positive response to lumbar branch block or denervation.

LIMITATIONS

For prescription use only.

The Neurolyser XR is not designed, sold, or intended for use except as described in the indications for use and is contraindicated for use in patients with the following conditions:

- Pregnant or breastfeeding

- History of lumbosacral spine surgery
- Metal hardware or foreign objects at lumbrosacral spine
- Extensive scarring at treatment area
- Uncontrolled coagulopathy
- Osteoporosis with absolute risk of spinal fracture at > 10% over 10 years
- Rheumatologic disease causing spine pain, currently receiving active treatment

The patient target group is adults only with chronic, facet-mediated low back pain.

This Neurolyser XR is for use only by qualified medical personnel trained in the safe use of interventional pain management procedures and in the proper use of the Neurolyser XR.

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

DEVICE DESCRIPTION

The Neurolyser XR (NXR100) system is a non-invasive portable high intensity focused ultrasound system made of a single sonication platform used to induce peripheral neural tissue ablation at specific anatomical targets in the proximity of a bony structure. The energy delivered into a focal anatomic target creates thermal ablation in a non-sterile setting without piercing the skin.

The Neurolyser XR is composed of the following components: Control Unit, Ultrasonic Transducer, Patient Halt Button, Coupling Accessory (Gel Pad), Positioner and Aiming Apparatus ArUco Board, Image Grabber, and Imaging Workstation. The Control Unit generates and controls the electrical pulse to drive the Neurolyser XR high intensity Transducer. The Transducer converts electrical energy from Control Unit and delivers acoustic energy to the target location. The coupling accessory (gel pad) provides acoustic coupling for efficient energy transmission between the Transducer and the target anatomy. The Positioning Accessory contains the ArUco board and a Targeting Aim which help position the Transducer in real time using optical and radiological markers.

The system is compatible with an X-ray guidance system (fluoroscopy) to allow accurate anatomical identification and targeting to achieve the ablation of the targeted neural tissue. The Neurolyser XR operates with any existing C-arm (Fluoroscopy) system.

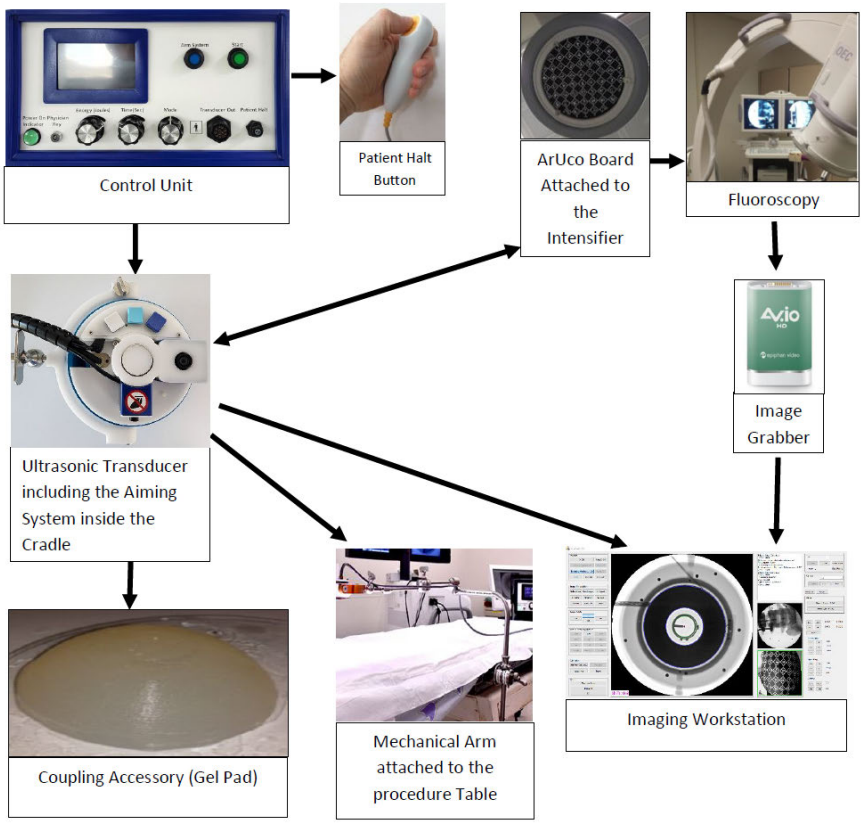


Figure 1: System block diagram of the Neurolyser XR device components and how they interact: Control Unit, Ultrasonic Transducer, Patient Halt Button, Coupling Accesory (Gel Pad), Positioning and Aiming Apparatus, ArUco Board, Image Grabber, and Imaging Workstation. The Fluoroscopy System is not part of the Neurolyser XR device. The Neurolyser XR operates with any existing C-arm (Fluoroscopy) system.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY

The hydrogel gel pad component of the Neurolyser XR is considered a surface device in limited (≤ 24 hours) contact with intact skin. As such, its biocompatibility evaluation was conducted in accordance with ISO 10993-1:2018, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process," and the FDA guidance "Use of International Standard ISO-10993, 'Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process". For a limited duration intact skin contact device, the gel pad was evaluated for cytotoxicity, sensitization, and irritation/intracutaneous reactivity. The cytotoxicity, sensitization, and irritation/intracutaneous reactivity endpoints were assessed from testing submitted in K950943 for the cleared Aquaflex Ultrasound Gel Pad by Parker Laboratories (previously cleared under the name Ultra Ease Gel Pad) for a different intended use.

Table 1. Biocompatibility Evaluations for the Neurolyser XR

Test	Test Method	Results
Cytotoxicity	ISO 10993-5:2009, Agar Overlay Method	Per Agar Overlay, there was indication of reactivity. [1]See note below.
Sensitization	ISO 10993-10:2002, Beuhler Dermal Sensitization	Non-sensitizing
Intracutaneous Reactivity	ISO 10993-10:2002, Primary Skin Test	Non-irritant

[1]The toxicological assessment identified parabens as the cause of cytotoxicity indicators; however, the amount of parabens in the pad still result in favorable MOS (Margin of Safety) values when product is used as intended. Hence, no adverse effects are expected, and no adverse effects have been identified in Post Market Surveillance.

SHELF LIFE/STERILITY

The patient-contacting coupling accessory (gel pad) provided by Parker Laboratories is supplied non-sterile and labeled for single-use (disposable) and are heat sealed in individual paper/poly/foil/poly pouches. The gel pads are individually labeled and dated with a 2-year expiration date from testing submitted in K950943 for the cleared Aquaflex Ultrasound Gel Pad by Parker Laboratories (previously cleared under the name Ultra Ease Gel Pad) for a different intended use.

The patient halt button is a reusable component contacting intact skin, requiring cleaning and disinfection between patient use. The recommended product (CaviWipe) is an EPA registered disinfectant. The directions for use in the Neurolyser XR labeling refer users to follow the reprocessing instructions, warnings, and precautions in the CaviWipe product labeling. The Positioning and Aiming Apparatus, Control Unit, Imaging Workstation, Imaging Workstation Screen are reusable, non-patient contacting components. The instructions recommend cleaning the screen with LCD cleaner per the manufacturer's instructions.

MAGNETIC RESONANCE (MR) COMPATIBILITY

MR compatibility testing was not conducted for the Neurolyser XR because the materials of composition are known to be MR unsafe.

PERFORMANCE TESTING – BENCH

Non-clinical bench testing was performed to demonstrate that the device can function as intended under clinical conditions of use and mitigate the risks to health (e.g., adverse tissue reaction, tissue injury, use error). The non-clinical bench testing performed are presented in Table 2. All tests met pre-defined acceptance criteria.

Table 2. Summary of Non-Clinical Bench Testing for the Neurolyser XR

Test	Test Purpose and Description
Acoustic Power	Acoustic output power was quantified using a radiation force balance. Maximum system output was found to be 40W. This protocol was described in detail and is performed as a part of ongoing maintenance semi-annually on every transducer using the FUSMobile acoustic calibration procedure following an IEC- 61161 compliant radiation force balance setup.
Acoustic Pressure Field Mapping	Acoustic pressure field mapping was conducted to characterize the acoustic field generated by an incoherent Neurolyser XR transducer array using a heterodyne interferometer system. The focal dimension measurements matched the simulation results to support accurate acoustic mapping.
Skin Heating Simulation	The possibility of adverse skin heating effects during treatment was determined with K-wave-based simulation. This simulation indicated little risk due to skin heating at operating parameters using a conservative approximation.
Thermal Performance	Thermal ablation accuracy around focal regions at bone/tissue interfaces (lumbar medial branch) was determined using a K-wave and bio-heat transfer simulation package. Results indicated thermal ablation occurred with controllable dose-dependent outcomes supporting consistent therapeutic thermal lesion production under the proposed clinical ultrasound output levels.
Inertial Cavitation	Peak pressures were measured at the acoustic focus using max acoustic power output. Resulting pressure at the acoustic foci were below the cavitation risk threshold indicating a low likelihood of cavitation.
Software/Cybersecurity	Software verification and validation testing and documentation was provided according to a Enhanced Documentation Level per FDA's guidance document, "Content of Premarket Submissions for Software Contained in Medical Devices," published June 2023, to demonstrate that the device software performs as intended.

	Cybersecurity testing and documentation was provided according to the recommendations per FDA's guidance document, "Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions," published September 2023, to demonstrate that the device is cybersecure.
Electrical Safety	Electrical safety risk analysis, testing and documentation was provided according to IEC 60601-1 (General) and IEC 60601-2-62 (high intensity focused ultrasound) standards.
Electromagnetic Compatibility (EMC)	EMC risk analysis, testing and documentation was provided according to IEC 60601-1-2 standards.
Human Factors and Usability	A usability study involving 15 experienced pain management physicians was conducted to evaluate the design and usability of the Neurolyser XR for intended users, uses, and use environment. The study evaluated the device in the final, finished form following the User Manual. Critical and non-critical tasks were performed with high success rates (99.5% and 96.0%, respectively), and error rates were minimal (0.5% for critical tasks, 2.4% for non-critical tasks). No systemic patterns of difficulty were observed.

PERFORMANCE TESTING – ANIMAL

Three animal studies were performed to evaluate the in vivo safety and effectiveness of the Neurolyser XR for ablation at the medial branch of the spinal nerves.

Non-Good Laboratory Practices (non-GLP) Porcine Chronic Study

A non-GLP chronic study was performed to evaluate the safety and effectiveness of the Neurolyser XR device following thermal lesion creation at medial branch locations in six pigs using two different energy levels over extended follow-up periods. The study was conducted to assess targeting accuracy, lesion characteristics, bone effects, and long-term safety through clinical follow-up, histopathology, and CT evaluation.[1]

[1] Aginsky R, LeBlang S, Hananel A, et al. Tolerability and feasibility of X-ray guided non-invasive ablation of the medial branch nerve with focused ultrasound: preliminary proof of concept in a pre-clinical model. Ultrasound in Medicine & Biology. 2021;47(3):640-650.

Six pigs were divided into two energy groups, with three pigs receiving 1500 J and three pigs receiving 2500 J. Three thermal lesions were created at the right L2, L3, and L4 medial branch locations in each pig. Animals were followed for varying periods (one week, one month, and three months) to evaluate lesion progression and safety outcomes.

The study demonstrated successful thermal lesion creation at the targeted anatomical locations with treatment times of approximately 5 minutes per lesion. Targeting accuracy was confirmed through macro pathology examination, showing the system performed within the requirements of the targeted anatomy. Throughout the follow-up period, no evidence of neurological deficits was observed, with all six pigs remaining alert, and responsive. Minor adverse events included small areas of erythema in two pigs related to X-ray sticker placement, which resolved without lasting effects. CT evaluation confirmed that bone density alterations occurred only in targeted areas with no compromise of bone around the spinal canal and no fractures observed. Histopathological evaluation of spinal roots showed no evidence of thermal damage to sensitive structures. The study concluded that both energy levels were adequate for safety.

Good Laboratory Practices (GLP) Porcine Safety Study

A GLP safety study was performed to assess the safety of the Neurolyser XR device following activation when guided to the medial nerve branch area of lumbar vertebrae in pigs. The study evaluated safety outcomes over a five-day observation period with histopathological assessment.

Nine female pigs were divided into three groups: two treatment groups receiving different energy levels (1500 J and 2000 J representing clinical parameters and worst-case lesion size, respectively) and a reference group treated with radiofrequency ablation. All animals were observed for five days post-procedure, after which exposure sites were collected for gross examination and histopathological evaluation by a qualified pathologist to assess damage to the medial branch of the nerve and the spinal cord.

The study demonstrated a safety profile with no abnormal clinical signs observed throughout the observation period. No neurological effects or absence of reflexes were observed, and histopathological examination revealed no microscopic abnormalities in any spinal cord samples. The evaluation showed that most damaged nerves were found in ablation sites while most normal nerves were found in samples without ablation sites or away from them, although significant variability was present within the ablations for all 3 groups. The study concluded that activation of the Neurolyser XR when guided to the medial nerve branch of lumbar vertebrae resulted in no adverse neurological effects and could be considered safe for use.

GLP Porcine Effectiveness Study

A GLP effectiveness study was performed to assess both the safety and lesion effects of the Neurolyser XR device following activation when guided to the medial nerve branch of lumbar vertebrae in pigs, with consideration for its projected use as a neural ablation

device.[2] The study evaluated effectiveness outcomes over a two-day observation period with comprehensive histopathological assessment.

Twelve female domestic pigs were divided into four groups: three treatment groups receiving different energy levels (1000J, 1500J, and 2000J representing clinical parameters and worst-case lesion size) and a reference group treated with radiofrequency ablation. Animals were observed for two days post-application, after which exposure sites were collected for gross examination and histopathological evaluation by a sponsor-selected pathologist.

The study demonstrated an adequate safety profile as histopathological examination showed no microscopic abnormalities in any spinal cord samples, with ablation sites identified in the majority of samples. The study showed a trend of necrotic borders representing boundaries of lethal damage, but was limited by a short (2-day) follow up time period prior to termination. The study showed lower but comparable ablation to reference controls at clinical energy levels, as the rate of confirmed nerve damage in ablation sites per pathology reports was 29%, 41%, and 29% at 1000J, 1500J, and 2000J, respectively, while the radiofrequency control group showed a rate of 50%.

SUMMARY OF CLINICAL INFORMATION

Clinical data used to support the De Novo for the Neurolyser XR included a prospective, multicenter, global, double-blind, randomized, sham-controlled, pivotal study to evaluate device safety and effectiveness in adult patients between 45 and 85 years of age who were diagnosed with unilateral or bilateral chronic lumbar zygapophyseal joint pain. Subjects were randomized in a 1:1 ratio between treatment and sham arms and were blinded to the treatment assignment. The study enrolled a total of 90 subjects including 10 roll-in subjects and 80 randomized subjects. Of the randomized subjects, 41 subjects received Neurolyser XR treatment and 39 subjects received sham treatment.

Follow-up Schedule

Patient follow-up was performed with phone interviews on post-procedure days 2 and 14, and office visits at 1 week and 1, 3, and 6 months.

Blinding

Participants enrolled in the study, all site clinical personnel, and those involved in evaluating safety and/or effectiveness data were blinded to the treatment assignment. In an attempt to maintain blinding, subjects in both study groups received standardized information and instructions prior to and during the procedure and both the Treat and Sham modes of the control unit reported visual power output and accumulated time and energy.

[2] Gofeld M, Tiennot T, Miller E, et alFluoroscopy-guided high-intensity focused ultrasound ablation of the lumbar medial branch nerves: dose escalation study and comparison with radiofrequency ablation in a porcine modelRegional Anesthesia & Pain Medicine 2025;50:429-436.

Crossover

The study permitted bidirectional subject crossover between 1-3 months following the index procedure for participants deemed as non-responders using the definition below. In the event of crossover, subjects underwent the crossover procedure and reinitiated follow starting from the date of the crossover procedure as dictated by the follow up schedule. Subjects who crossed over were deemed failures in the primary effectiveness analysis using the assumption that a non-responder at the time of crossover would continue to be a non-responder at the primary endpoint timepoint of 6 months.

Inclusion and Exclusion Criteria

Subjects were eligible for enrollment in the study if they met all of the following inclusion criteria:

- Age 45 to 85 years old, legally able and willing to participate in the study and all follow-up visits
- Able and willing to complete the research questionnaires and to communicate with investigator and research team
- Individual with current bilateral or unilateral low back pain of > 6 months duration
- Individual whose back pain is alleviated by recumbency or comfortable sitting position
- Individual presenting with a) a positive (>80% pain relief) to a previous, double, lumbar medial branch block (within the last 12 months) and/or b) with a positive (>70% pain relief lasting more than 6 months) to the most recent lumbar facet thermal radiofrequency denervation
- Average low back pain score of 6 or higher in the last month (on 0-10 scale) with activity

Subjects were not eligible for enrollment in the study if they met any of the following exclusion criteria:

- Individuals who are pregnant or breastfeeding
- Individuals younger than 45 or older than 85 years
- BMI greater than 40, or individuals with at least one of the planned targets outside the Neurolyser XR treatment envelope as seen on treatment day on a lateral X-ray scan taken before the treatment.
- Individuals presenting with neurological deficits (including lumbosacral radiculopathy but not solitary radicular pain)
- Individuals with history of lumbar or lumbosacral spine surgery
- Individuals who have had lumbar radiofrequency neurotomy in the past 6 months
- Individuals with history of lumbar spine pathology that may increase procedural risk and/or influence symptoms and/or generate unrelated adverse event (per investigator's discretion)

- Individuals presenting with any severe medical condition preventing them from participation (per investigator's discretion) (Example: inability to lay prone)
- Individuals with extensive scarring of the skin and tissue overlying the treatment area
- Individuals enrolled in or planned to be enrolled in another clinical trial during the duration of this research project
- Any Individuals with an uncontrolled coagulopathy
- Individuals with known osteoporosis with absolute risk of spinal fracture of > 10% over 10 years
- Any Individuals with a history of malignant disease in the past five years
- Individuals with rheumatologic diseases causing spine pain that are currently receiving active treatment including steroids, disease modifying drugs, biological agents or immunosuppressants
- Individuals known for concomitant psychiatric disorders, excluding compensated mood disorders
- Individuals with first-degree family member already enrolled in this study
- Individual who is scheduled for any interventional/surgical procedure within 6 months from the treatment date excluding trivial surgeries (e.g., cataract, carpal tunnel release)
- Individuals diagnosed with co-morbid multifocal chronic pain (e.g. fibromyalgia, generalized osteoarthritis)
- Individuals with other chronic pain that is 2 or more points higher on the NRS score than the participants low back pain
- Individuals who have had a steroid injection within the last 2 months from date of enrollment at the location of the planned treatment
- Any individual with a history of substance abuse per the PI discretion
- Any individual with a current open legal case related to the individual's, worker's compensation claim

Primary Effectiveness Endpoint

The primary effectiveness endpoint in this trial is "Responder" status at 6 months scored dichotomously as Responders or non-responders. Responders were defined as follows:

1. Reduction in average Numerical Rating Scale (NRS) from baseline to 6-months post-treatment of at least 2 points,
   AND
2. No increase in pain medication usage, quantified by "morphine equivalent units," of ≥ 25% at 6-months post-treatment relative to baseline.

OR

1. No increase in average NRS from baseline to 6-months post-treatment of at least 2 points,
   AND

2. Decrease in pain medication usage, quantified by "morphine equivalent units," of ≥ 25% at 6-months post-treatment relative to baseline.

Subjects who did not meet either of the above criteria were adjudicated as non-Responders. The analysis tested the following hypothesis:

$$H_0: R_{Neurolyser} \leq R_{Sham}$$
$$H_1: R_{Neurolyser} > R_{Sham}$$

where $R_{Neurolyser}$ and R_{Sham} are the 6-month response rates of the Neurolyser XR and Sham groups, respectively. Success would be declared if the two-sided group p-value fell below 0.05.

Safety Endpoints:
The primary safety endpoint evaluated the incidence of severe or serious device-related adverse events obtained in the treat arm.
Example of serious device related AEs included,

- Persistent severe (NRS > 6/10) new localized back pain or new leg pain observed immediately after the procedure and remained unresolved for more than a months
- Any new motor deficit (leg weakness) observed immediately after the procedure and remained unresolved for more than a months
- 3rd degree skin burn larger than $1cm^2$

Enrollment and Subject Disposition:
A total of 106 subjects signed the study informed consent and were screened for the study of which 8 patients did not meet the study eligibility criteria. Of the 98 eligible subjects, 10 roll-in subjects received the Neurolyser XR treatment, 44 subjects were assigned to each of the treatment and sham arms. In each arm, 4 subjects did not meet technical eligibility of skin to target depth requirements which was determined after randomization. One subject that was randomized to the Neurolyser XR group mistakenly received the sham treatment, and 2 subjects randomized to the sham group mistakenly received the Neurolyser XR treatment. Ultimately, forty-one randomized subjects received Neurolyser treatment and 39 subjects received the sham treatment.

Clinical Study Results

Subject Disposition
Subject disposition is shown in Figure 2. Of the 41 subjects who received the Neurolyser XR treatment, 30 subjects had primary effectiveness endpoint data at 6 months where 6 subjects crossed over to the sham treatment and were defined as failures and five subjects had missing primary endpoint data at 6 months. Of the 39 subjects in the sham group, 12 subjects had primary effectiveness endpoint data at 6 months where 26 sham subjects crossed over to the Neurolyser group and were considered failures and one subject had missing primary endpoint data at 6 months.

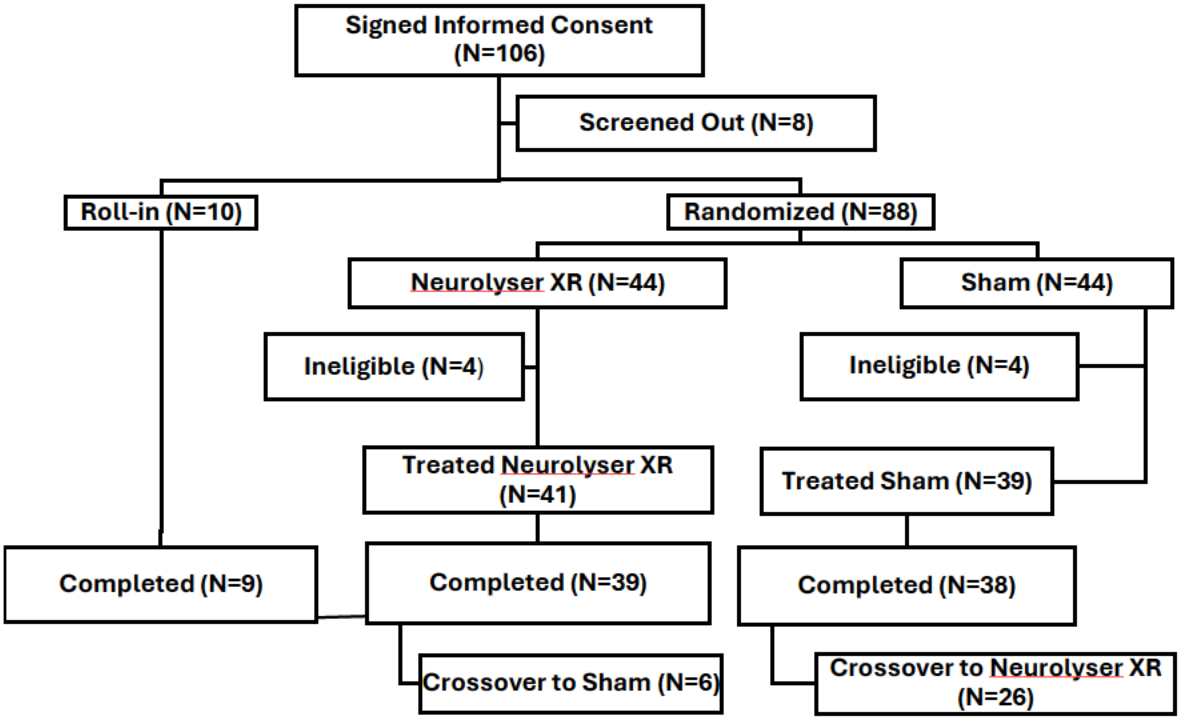


Figure 2. Study Subject Disposition Flowchart

Demographic Characteristics

The study demographics are shown in Table 3. Overall study enrollment was approximately even between genders with slightly more female participants (54% female vs 47% male). The mean age at baseline was 64.1 years and was similar between groups (64.6 in the Neurolyser XR vs 62.8 in the sham). BMI of the study population were between the range of 19 to 40 (kg/m^2) and were relatively consistent across study groups. The population was mostly White or Caucasian (80%) and also included 11.1% Black/African American and 5.6% Hispanic subjects. All but one participant reported at least one relevant medical history event of a confirmed diagnosis related to back pain. About 30% of participants had taken opioid medications for pain in the last 24 hours prior to screening.

Table 3. Study Participant Baseline Characteristics, Demographics, and Medical History

Parameter	Statistics	Roll-in	Neurolyser XR	Sham	All
Age (Years)	n	10	41	39	90
	Mean (SD)	66.8 (10.3)	64.6 (9.8)	62.8 (10.3)	64.1 (10.0)
	Median (Min, Max)	69.5 (48.0, 80.0)	65.0 (50.0, 83.0)	61.0 (47.0, 83.0)	63.5 (47.0, 83.0)
Weight (kg)	n	10	41	39	90
	Mean (SD)	83.2 (15.2)	82.7 (16.4)	81.7 (19.2)	82.3 (17.4)

Parameter	Statistics	Roll-in	Neurolyser XR	Sham	All
	Median (Min, Max)	84.8 (59.2, 114.6)	83.9 (49.0, 111.6)	82.1 (51.7, 129.7)	83.0 (49.0, 129.7)
Height (m)	n	10	41	39	90
	Mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
	Median (Min, Max)	1.7 (1.5, 1.9)	1.7 (1.5, 2.0)	1.7 (1.5, 1.9)	1.7 (1.5, 2.0)
BMI (kg/m^2)	n	10	41	39	90
	Mean (SD)	28.4 (4.2)	28.0 (4.1)	28.3 (5.1)	28.2 (4.6)
	Median (Min, Max)	28.6 (22.3, 35.7)	27.7 (20.4, 37.7)	29.1 (19.0, 40.0)	28.0 (19.0, 40.0)
Gender	Male	n=5, 50%	n =21, 51.2%	n =16, 41%	n =42, 46.7%
	Female	n=5, 50%	n =20, 48.8%	n =23, 59%	n =48, 53.5%
	Total	n=10, 100%	n =41, 100%	n =39, 100%	n =90, 100%
Relevant Medical History	n	n=10, 100%	n=41, 100%	n=38, 97.4%	n=89, 98.9%
Opioid medication within past 24 hours	n	n=3, 30%	n=12, 29.3%	n=12, 30.8%	n=27, 30%

Primary Effectiveness Endpoint

The pre-specified primary effectiveness analysis included 41 Neurolyser subjects and 39 sham subjects. The rate of treatment responders is shown in 4 which presents estimated response rates of 53% and 21% for Neurolyser XR and sham groups, respectively. These outcomes resulted in an odds ratio of 4.3 (p= 0.004), favoring the Neurolyser XR arm. This analysis considered all crossovers as automatic treatment failures and used multiple imputation for missing data that was due to reasons other than crossover.

As mentioned above, 30 subjects in the Neurolyser group and 12 subjects in the sham group had primary effectiveness endpoint data at 6 months. Subject crossover rates were 14.6% and 66.7% for the Neurolyser XR and sham groups, respectively. This analysis assumes that subjects identified as non-responders at the time of crossover would have continued to be non-responders at the 6-month primary endpoint.

Table 4. Primary Effectiveness Analysis: Treatment Responder Rate with Multiple Imputation

	Treatment Group		
Statistics	**Neurolyser XR (N=41)**	**Sham (N=39)**	**Odds Ratio**
Number of Responders, n (min-max)[1]	19 - 23	8	
Estimated Response Rate / OR	0.53	0.21	4.34
95% Confidence Interval	(0.37, 0.68)	(0.11, 0.36)	(1.58, 11.90)
P-Value			0.004

[1] Number of Responders is presented as a range due to different imputation methods used.

Three sensitivity analyses were conducted to assess the robustness of the primary effectiveness endpoint as shown in Table 5 and 6. Sensitivity analyses were conducted considering a Last Observation Carried forward (LOCF) (sensitivity analysis #1), an analysis considering only observed data at 6 months (sensitivity analysis #2), and by performing the primary analysis prior to the crossover window (sensitivity analysis #3). With the exception of sensitivity analysis #2, the analyses trended favorably for the Neurolyser XR showing a robust outcome. It should also be noted that the sensitivity analysis #2 is associated with uncertainty from small subject numbers which limits interpretability of this analysis.

Table 5. Analysis Methodology and Assumptions

Analysis	**Handling of Crossovers**	**Missing Data Approach**	**Key Assumptions**
Primary Effectiveness Analysis	Automatic failure	Multiple imputation	Non-responder status stable through to 6 months
Sensitivity #1 (LOCF)	Last pre-crossover value[1]	Last Observation Carried Forward	Stable response trajectories and non-responder status stable through to 6 months
Sensitivity #2 (Observed Data Only)	Excluded	Exclude missing data	Missing completely at random
Sensitivity #3 (Pre-Crossover Window)	Not applicable	Minimal (95% available)	Early endpoints reflect those at 6 months

[1] Since crossover subjects were required to meet non-responder criteria, crossovers would be considered failures.

Table 6. Primary and Sensitivity Analyses Summary

Analysis Type	Method	N, (%) Responder Neurolyser	N, (%) Responder Sham	p-value	Odds Ratio (95% CI)	N, Sample Size (Neurolyser/ Sham)
Primary Effectiveness Analysis	Crossovers considered failures & MI[1] used for missing data	19-23 (53%)	8 (21%)	0.004	4.3	41/39
Sensitivity #1 (LOCF)	Last observation carried forward	19-23 (53%)	12-12 (31%)	—	—	41/39
Sensitivity #2 (Observed Data Only)	Exclude crossovers/ missing	18 (60%)	8 (67%)	—	—	30/12
Sensitivity #3 (Pre-Crossover Window)	1-month endpoint, Crossovers imputed LOCF & MI[1] used for missing data	26 (63%)	18 (46%)	—	—	41/39

[1] MI = multiple imputation

Subgroup analyses were conducted to assess the impact of baseline characteristics on the likelihood of crossover. Table 7 presents descriptive statistics of participants' baseline characteristics split by treatment group and crossover status. In the Neurolyser XR group, participants who crossed over were on average older than participants who did not crossover(70.5 years vs 63.6 years, respectively). In the sham group, participants who crossed over were on average younger compared to participants who did not crossover(59 years vs 70 years, respectively). The average age for the combined group of all crossover and non-crossover participants is similar, with an average of 61 years and 65.5 years for crossover and non-crossover, respectively. For all the remaining covariates examined, the distributions of the covariates obtained in the subset of crossover participants and non-crossover participants were similar.

Table 7. Study Participants Subgroup Analysis

	Neurolyser XR		Sham		All	
Statistics	**Crossover (N=6)**	**Non-Crossover (N=35)**	**Crossover (N=26)**	**Non-Crossover (N=13)**	**Crossover (N=32)**	**Non-Crossover (N=48)**
Age (years)						
n	6	35	26	13	32	48
Mean (SD)	70.5 (6.50)	63.6 (9.94)	59.1 (8.47)	70.4 (9.83)	61.2 (9.23)	65.5 (10.27)
Median	71.5	63.0	57.5	69.0	59.5	64.5
25th, 75th Percentiles	68.0, 72.0	54.0, 73.0	52.0, 65.0	63.0, 81.0	53.0, 69.0	55.5, 74.5
Min, Max	60, 80	50, 83	47, 79	54, 83	47, 80	50, 83

	Neurolyser XR		Sham		All	
Age Group 1, n (%)						
=<63	1 (16.7)	18 (51.4)	19 (73.1)	4 (30.8)	20 (62.5)	22 (45.8)
>63	5 (83.3)	17 (48.6)	7 (26.9)	9 (69.2)	12 (37.5)	26 (54.2)
Sex, n (%)						
Female	3 (50.0)	17 (48.6)	16 (61.5)	7 (53.8)	19 (59.4)	24 (50.0)
Male	3 (50.0)	18 (51.4)	10 (38.5)	6 (46.2)	13 (40.6)	24 (50.0)
Race, n (%)						
Black/African American	2 (33.3)	4 (11.4)	1 (3.8)	3 (23.1)	3 (9.4)	7 (14.6)
Caucasian/White	4 (66.7)	29 (82.9)	19 (73.1)	10 (76.9)	23 (71.9)	39 (81.3)
Hispanic	0	0	5 (19.2)	0	5 (15.6)	0
Other	0	2 (5.7)	1 (3.8)	0	1 (3.1)	2 (4.2)
BMI Group, n (%)						
Normal weight (BMI =< 25)	2 (33.3)	10 (28.6)	7 (26.9)	1 (7.7)	9 (28.1)	11 (22.9)
Obese (BMI > 30)	2 (33.3)	9 (25.7)	9 (34.6)	5 (38.5)	11 (34.4)	14 (29.2)
Pre-obese (25 < BMI =< 30)	2 (33.3)	16 (45.7)	10 (38.5)	7 (53.8)	12 (37.5)	23 (47.9)
Baseline NRS Group, n (%)						
6	1 (16.7)	16 (45.7)	9 (34.6)	4 (30.8)	10 (31.3)	20 (41.7)
7	1 (16.7)	9 (25.7)	9 (34.6)	4 (30.8)	10 (31.3)	13 (27.1)
8+9	4 (66.7)	10 (28.6)	8 (30.8)	4 (30.8)	12 (37.5)	14 (29.2)
Number of Treated Lesions Group, n (%)						
<6	2 (33.3)	5 (14.3)	7 (26.9)	4 (30.8)	9 (28.1)	9 (18.8)
6	4 (66.7)	24 (68.6)	17 (65.4)	9 (69.2)	21 (65.6)	33 (68.8)
>6	0	6 (17.1)	2 (7.7)	0	2 (6.3)	6 (12.5)

Effectiveness Conclusion

This study was limited by small sample sizes at the time of the 6-month primary effectiveness endpoint due to high crossover rates occurring prior to the endpoint assessment. Primary endpoint outcomes were assigned as failures for crossover patients which assumes non-responders at the time of crossover will continue to be non-responders at 6 months. However,

sensitivity analyses generally showed favorable trends of benefit for the Neurolyser XR group when compared to the sham group. Additionally, the pre-specified primary analysis demonstrated a statistically significant difference between the Neurolyser XR and sham with an odds ratio of 4.34 ($p = 0.004$). These results suggest meaningful benefit of the Neurolyser XR over sham.

Safety Results

In the Neurolyser XR group 13 subjects (31.7%) experienced at least one Adverse Event (AE), with 14 AEs in total. In the Sham group 7 subjects (17.9%) experienced at least one AE, with 7 AEs in total. All AEs except one were treatment-emergent AEs (i.e. started on the day of the procedure onwards). Four "possible" device related AEs occurred in the Neurolyser XR treatment group, however these were all mild and resolved within the study duration (Table 8). Three serious AEs (SAEs) occurred in 3 subjects in the Neurolyser XR group, and one SAE occurred in the Sham group. None of the SAEs were related to the study device or procedure. One death occurred in the study from cardiopulmonary arrest, disseminated intravascular coagulation, septic shock, and bacterial pneumonia after a fall at home unrelated to the study. None of the subjects who underwent active Neurolyser treatment (roll-in, Neurolyser XR as the first treatment or as a crossover treatment) experienced serious device related AEs. These results support that the Neurolyser device is generally safe in the intended population.

Table 8. Summary of Treatment-Emergent Adverse Events (TEAEs)

System Organ Class Preferred Term	**Number of Subjects (%) Neurolyser XR Group N=41**	**Number of Subjects (%) Sham Group N=39**
Total number of TEAEs labeled as "Possible"	4	0 (0%)
Number of subjects with at least one "Possible" TEAE	4 (9.8%)	0 (0%)
General disorders and administration site conditions	1 (2.4%)	0 (0%)
Burning	1 (2.4%)	0 (0%)
Nervous system disorders	3 (7.3%)	0 (0%)
Paresthesia	1 (2.4%)	0 (0%)
Tingling or numbness in right calf/foot	1 (2.4%)	0 (0%)
Left leg cramping with moderate tenderness	1 (2.4%)	0 (0%)

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

LABELING

The labeling includes instructions for use for the physician and satisfies the requirements of 21 CFR § 801.109 for prescription devices. The labeling also includes:

- Detailed description of the device technical parameters and all components.
- Detailed instructions on proper device setup, daily quality assurance, and procedure flow.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of high intensity focused ultrasound system for peripheral neural tissue ablation and the measures necessary to mitigate these risks.

Risks to Health	Mitigation Measures
Tissue injury resulting from: • Unintended tissue heating • Cavitation • Mistargeting or higher or lower energy than intended • Electrical shock • Acute radiation injury • User error	In vivo performance testing Non-clinical performance testing Software verification, validation, and hazard analysis Electrical safety testing Electromagnetic compatibility testing Labeling
Pain and nervous system disorders: • Skin discomfort or burns • Paresthesia • Ineffective treatment leading to worsening back pain	In vivo performance testing
Adverse tissue reaction	Biocompatibility evaluation

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the high intensity focused ultrasound system for peripheral neural tissue ablation is subject to the following special controls:

(1) In vivo performance testing must demonstrate that the device performs as intended to deliver ablative energy and evaluate all adverse effects, including adverse tissue injury to target and non-target tissues.
(2) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use, including:

(i) Characterization of acoustic pressure, including an acoustic map of relevant sections of the focal region, near-, and far-fields;
(ii) Characterization of overall acoustic power output and reproducibility;
(iii) Characterization of ultrasound induced focal temperature;
(iv) Demonstration of device positioning and targeting accuracy; and
(v) Assessment of ultrasound induced cavitation safety.

(3) Performance data must demonstrate the electrical safety and electromagnetic compatibility of the device.
(4) Software verification, validation, and hazard analysis must be performed.
(5) The patient-contacting components of the device must be demonstrated to be biocompatible.
(6) Labeling must include:
(i) Detailed description of the device components and technical parameters including targeting accuracy; and
(ii) A shelf life for single use components.

BENEFIT/RISK DETERMINATION

The probable risks of the device are based on data collected in a clinical study, animal studies, and nonclinical laboratories studies described above. The risks of the Neurolyser XR are tissue injury, nervous system disorder, worsening pain due to ineffective treatment, and adverse tissue reaction. These risks could occur from unintended tissue heating, device mistargeting or higher or lower energy delivered than intended, improper device use; and a device that is not biocompatible.

The probable benefits of the device are also based on data collected in nonclinical laboratory, animal, and clinical studies as described above. The benefits of the device are to safely and effectively deliver the appropriate therapeutic high intensity focused ultrasound energy to the target lumbar facet joint location for treatment of facet-mediated low back pain.

Sources of uncertainty in the benefits include the small sample sizes at the time of the 6-month primary effectiveness endpoint due to high crossover rates occurring prior to the endpoint assessment. This was addressed by assigning primary endpoint outcomes as failures for crossover patients which assumes non-responders at the time of crossover will continue to be non-responders at 6 months. Sensitivity analyses generally showed favorable trends of benefit for the Neurolyser XR group when compared to the sham group. Additionally, the pre-specified primary analysis demonstrated a statistically significant difference between the Neurolyser XR and sham with an odds ratio of 4.34 ($p = 0.004$) favoring the Neurolyser XR.

Additionally, the device provides treatment without the need for direct open surgery and allows repeat procedures throughout a patient's lifetime. Therefore, patients receiving treatment with Neurolyser XR may experience less procedural pain, discomfort, or anxiety, which may lower the barrier to treatment for those suffering from symptomatic chronic lumbar zygapophyseal joint pain.

Patient Perspectives

The primary outcome measures in the supportive clinical study were collected in part using patient reported outcomes. The patient reported primary effectiveness endpoint included average pain intensity measured using the Numerical Rating Scale (NRS).

Benefit/Risk Conclusion

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

> The Neurolyser XR is indicated for the thermal ablation (neurolysis) of the medial branch nerve of the lumbar facet joint(s) (L1 to L5) for the treatment of chronic, facet-mediated low back pain of at least 6 months duration and a confirmed diagnosis based on positive response to lumbar branch block or denervation.

The probable benefits outweigh the probable risks for the Neurolyser XR. 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 Neurolyser XR is granted and the device is classified under the following:

> Product Code: SGN
> Device Type: High intensity focused ultrasound system for peripheral neural tissue ablation
> Class: Class II
> Regulation: 21 CFR 882.4420