SETPOINT SYSTEM

SURGEON

INSTRUCTIONS FOR USE

Read all instructions, warnings and cautions carefully.

Failure to do so may damage the SetPoint System,
cause it to malfunction or perform poorly, and could result in injury.

If you have any questions about the information contained in the **SetPoint System Surgeon Instructions for Use** (Surgeon IFU), please **contact SetPoint Medical**.

All SetPoint System Instructions for Use (IFUs) are available on the SetPoint Medical website.

If you experience any incident or problem related to the SetPoint System
that may pose a safety risk, report it to SetPoint Medical immediately.

Contact

SetPoint Medical, Inc.
25101 Rye Canyon Loop
Valencia, CA 91355-5004
United States

setpointmedical.com
+1 661.339.7900
customersuccess@setpointmedical.com

Caution: Federal law restricts this device to sale by or on the order of a physician.

SURGEON QUICK REFERENCE GUIDE

SETPOINT SYSTEM PROCEDURE

CONFIRM CHARGER FIT

- Place the Charger around the patient's neck while they are seated upright.
- Verify that the magnetic latch closes and remains latched without discomfort.

See section **Charger Fit Confirmation** for more details.

SURGICAL PROCEDURE

See section **Implantation** for more details.

1. Nerve Exposure

- 1.2 in (3 cm) branch-free segment of left vagus nerve.

2. Implant Placement

- Place the Pod on the left vagus nerve.
- Insert the Implant into the Pod, with the head-shaped marking oriented rostrally.
- Visualize that nerve is seated through ends of Pod groove and is in Implant saddle.
- Ensure that no extra nerve branches or other structures are entrapped in Pod.

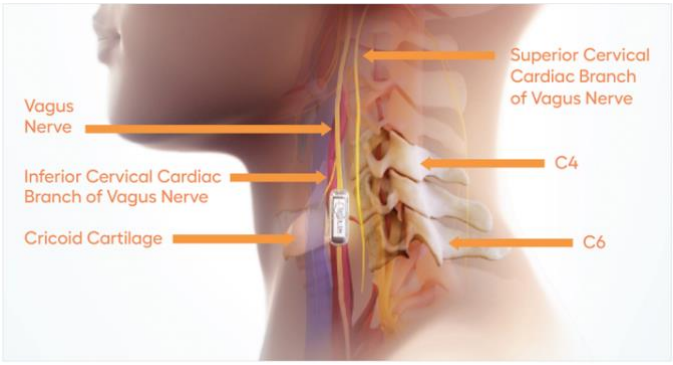
3. Closure

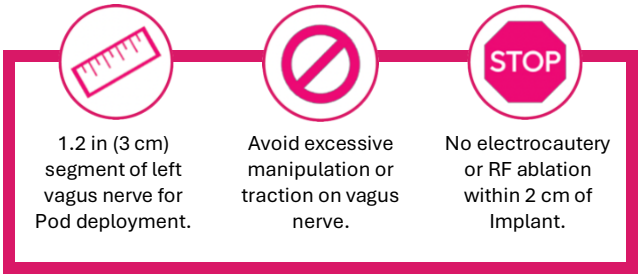
- Suture Pod through suture holes with non-absorbable 5-0 Prolene on a non-cutting needle and no more than 4 throws.
- Gently confirm Pod rotates and slides freely on the nerve.

IMPLANTATION LOCATION

- On the left cervical vagus nerve.
- Below both the inferior and the superior cervical cardiac branches.
- Ideally between the level of the C4 and C6 cervical vertebrae.

See section **Implantation Location** for more details.





It is important to read and understand the entire contents of the Surgeon IFU prior to use of the SetPoint System. Make sure to brief the patient on contraindications and warnings using section **Important Safety Information**.

SETPOINT® SYSTEM

SETPOINT MEDICAL

Table of Contents

Introduction

This **SetPoint System Surgeon Instructions for Use** (Surgeon IFU) describes the operation and intended use of the SetPoint System and the surgical procedure for implantation. The SetPoint System is to be used only by physicians who have reviewed and understand this Surgeon IFU.

The table below shows the SetPoint System model numbers for the parts of the system that are described in this IFU.

Device Name	Model Number
Implant	M01
Charger	E04
Docking Station	C01

Table 1 - Device Names and Model Numbers

To reorder the Implant, **contact SetPoint Medical** and request Manufacturer Part Number SPM001.

Indication for Use

The SetPoint System is indicated for use in the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response, loss of response or intolerance to one or more biological or targeted synthetic disease modifying antirheumatic drugs (b/tsDMARDs).

Pediatric Use

The SetPoint System is not intended for use in the pediatric population.

SetPoint System Description

The SetPoint System includes:

- The Implant (A) which is placed within a Pod (B) and implanted on the left vagus nerve in the neck (C)
- A Charger (D) with Docking Station (F)
- A Programmer (E)

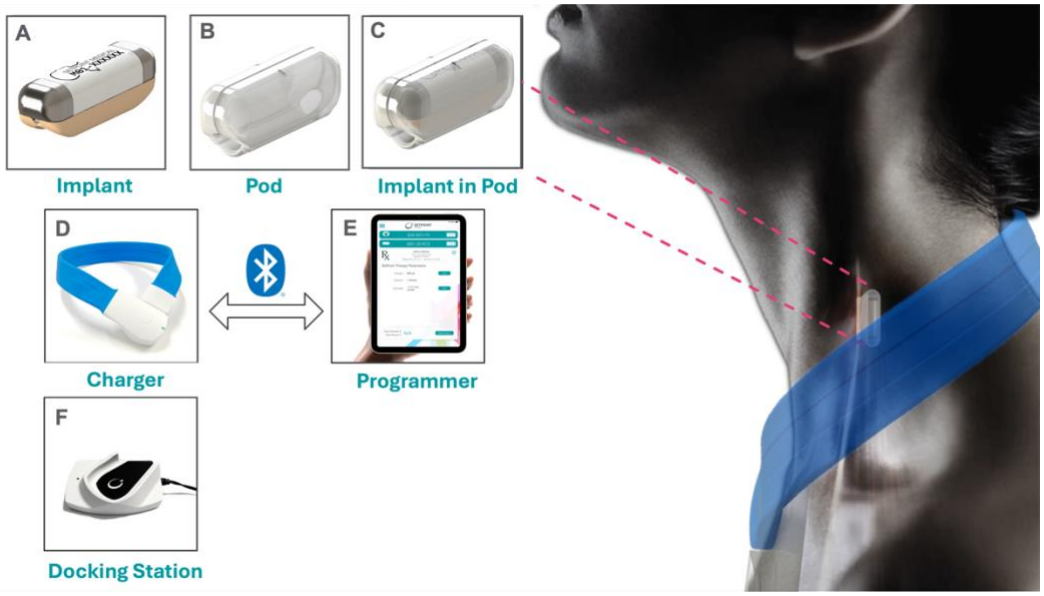


Figure 1 - SetPoint System and Components

Implant and Pod

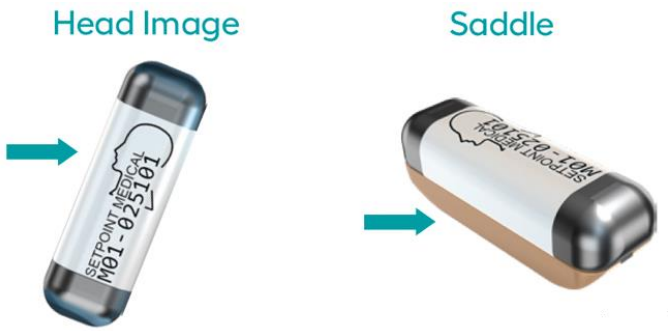


Figure 2 - Implant

The Implant is an integrated neurostimulation device. It is used to electrically stimulate the vagus nerve for 1 minute, every day. It is about 1 in (2.5 cm) long and weighs about 0.1 oz (3 g). The device is surgically implanted next to the vagus nerve on the left side of the neck. The Implant is placed inside a Pod, which is a flexible cover made of silicone. The Pod helps hold the Implant in place.

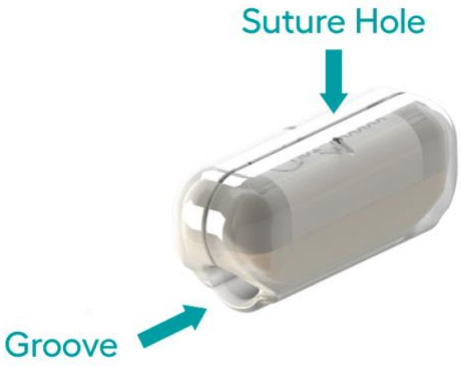


Figure 3 - Pod

The SetPoint System implantable components are supplied sterile, using an ethylene oxide (EO) process, and are only intended for single use. The Implant and two Pods (provided on plastic holders) are packaged in a sealed inner tray covered with an inner lid that prevents them from moving during transit (see **Figure 4**). The second Pod is provided for use only as a backup if the first Pod is damaged during deployment or while being sutured closed and is identical to the first Pod. The plastic holder is only intended for use during storage and must be discarded before the Pod is implanted. It is not meant for introduction into the surgical field.

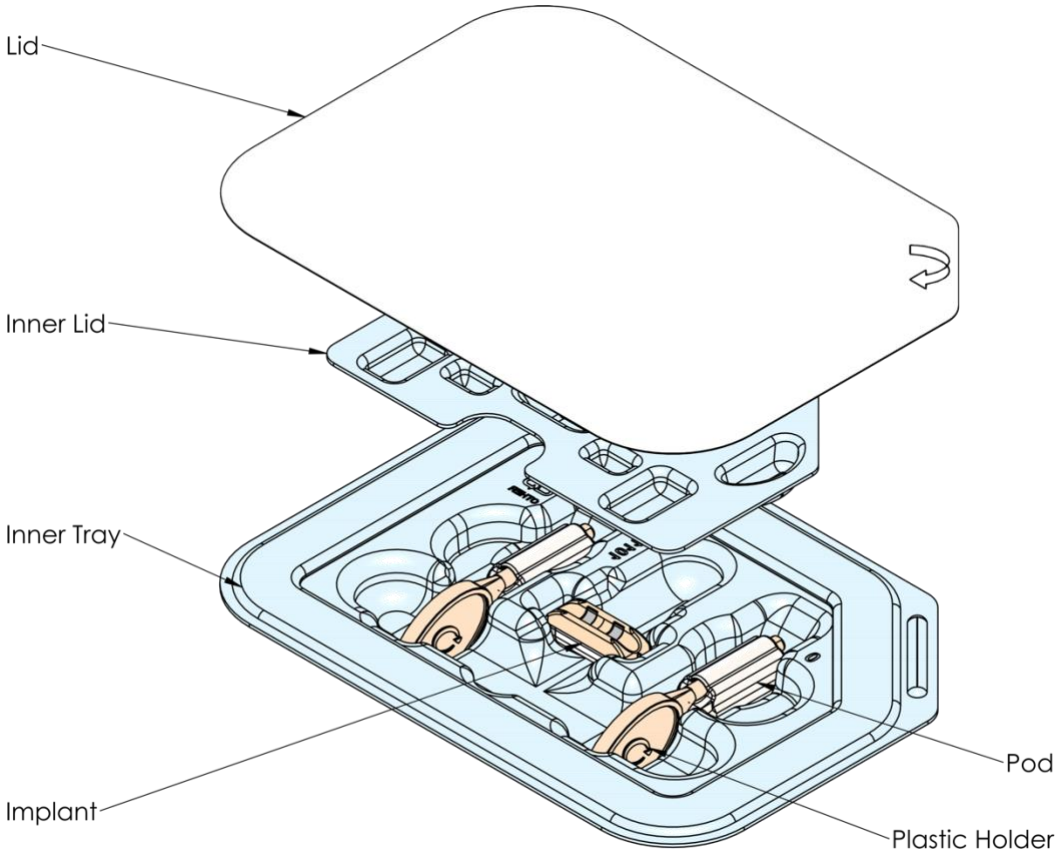


Figure 4 - Inner Tray Contents

The inner tray is packaged in a sealed outer tray, which displays the product labeling. The outer tray rests in a paperboard tray support and is packaged with a Patient ID Card inside a paperboard product box, which

also displays the product labeling. This product box is sealed with tamper evident labels. The product box must be stored within the following environmental conditions.

Temperature	Humidity	Altitude
50 to 104 °F (10 to 40 °C)	15 to 93 %RH	Up to 9,843 ft (3,000 m)

Table 2 – Storage Conditions

Charger and Docking Station

The Charger is a device worn around the patient's neck. It is used for charging the Implant at home and for programming the Implant at the clinic. The Docking Station is provided to charge and hold the Charger between uses.

For more information regarding the use of the Charger or Docking Station, please refer to the **SetPoint System Prescriber Instructions for Use** or **SetPoint System Patient Instructions for Use** which are available on the SetPoint Medical website.

Programmer

The Programmer is an app installed on an Apple iPad® that is only used by a trained healthcare professional. It is used with the Charger to program the Implant or to turn off or resume stimulation, if necessary. Additionally, it gives the healthcare professional information about the use of the Implant and Charger, such as how many doses have been delivered or missed, and Implant battery charge levels.

For more information regarding the use of the Programmer, please refer to the **SetPoint System Prescriber Instructions for Use** which is available on the SetPoint Medical website.

Patient Identification (ID) Card

The Patient ID Card is included in the Implant packaging. The Patient ID Card should be filled out per instructions that accompany the card (see **Figure 5**) and provided to the patient after the surgery, and before they leave the hospital. Device information, such as model number, serial number and device identifier, can be completed using one of four device stickers provided on the outer tray label in the Implant packaging (see **Figure 6**). Patients should be instructed to always have their Patient ID Card on hand and present it during security screenings, such as at airports. Additionally, the QR code on the card provides access to critical information regarding the Implant, which is necessary to ensure that any treatments are compatible with it. Instruct the patient to always present the Patient ID Card to healthcare professionals, dentists, or estheticians before pursuing any additional medical, medical imaging or beauty treatments. Neglecting to inform these professionals about the Implant may cause harm to the SetPoint System and/or may lead to complications with the treatment. If the patient changes their doctor or rheumatologist managing the SetPoint System, or loses their card, they should **contact SetPoint Medical for a replacement card**.

Figure 5 - Sample Patient ID Card (Front and Back)

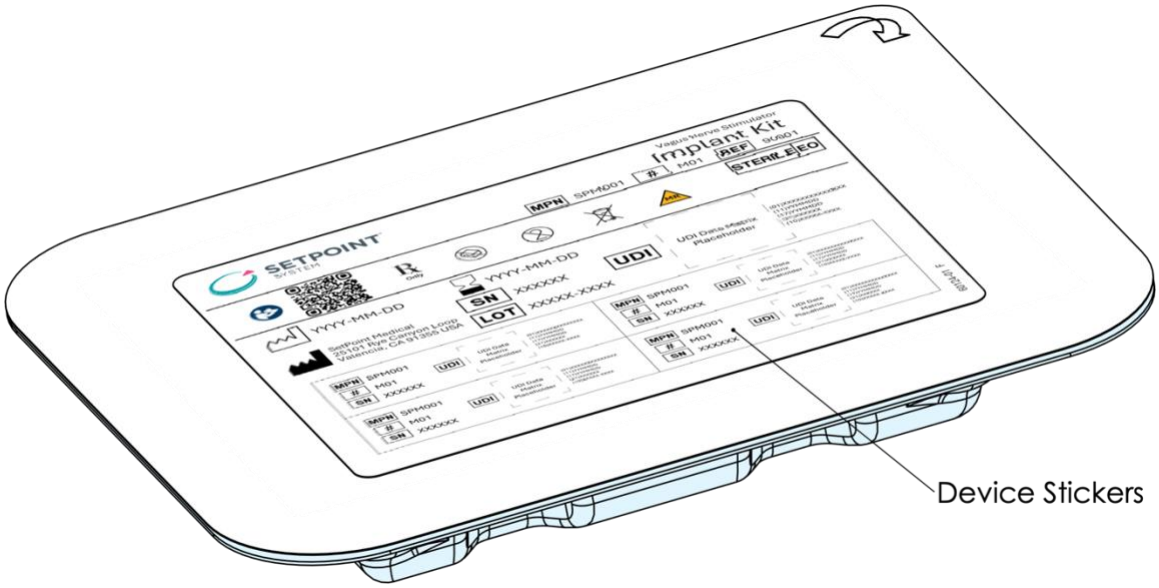


Figure 6 - Device Stickers on Outer Tray Label

Important Safety Information

Read all instructions, warnings and cautions carefully. If you have any questions, **contact SetPoint Medical**. If you do not follow these guidelines, the SetPoint System could get damaged, not work correctly, and/or result in harm.

Contraindications

There are certain situations in which the SetPoint System should not be used because the risk(s) are greater than the potential benefit(s).

The SetPoint System should not be used:

- If the patient has had certain health procedures that would interfere with how the device works, for example,
  - If they have had a bilateral or left cervical vagotomy.
  - If they have had their spleen removed (splenectomy).
- If you determine that it might not be safe for them to have the surgery, for example,
  - If they have spine disease in their neck that makes it risky to place a breathing tube (intubate).
  - If they cannot be safely given anesthesia for surgery.
- If they cannot safely use the SetPoint Charger, for example,
  - If their neck is too large to wear the SetPoint Charger.
  - If they have a pacemaker or a defibrillator implanted.

Warnings & Precautions

It is important that both you and the patient use the SetPoint System safely to avoid injury or damage to the SetPoint System or other devices. Here are some key safety tips:

- Instruct the patient to always present the Patient ID Card, prior to undergoing any treatment or diagnostic procedure, to healthcare professionals and providers such as physicians, dentists, imaging technicians (e.g., MRI, X-ray, computerized tomography), physical or occupational therapists, estheticians and beauty-care specialists. Failure to present the Patient ID Card may result in a treatment or procedure-related complication and/or may damage the SetPoint System (see **Medical Imaging Warnings** below).
- Instruct the patient not to scuba dive or enter a hyperbaric chamber after receiving the Implant. The safety of high pressure has not been established, and these conditions could damage the device.
- Do not use the Implant or Pod if either device shows damage, the packaging shows signs of significant damage, the sterile packaging is breached, the tamper evident label indicates that the package has been opened, or if the product is beyond its expiration date. If you do, you might implant a non-functional device or one with compromised sterility.
- Do not over-manipulate the vagus nerve throughout the surgical procedure. If you do, it may result in adverse effects such as hoarseness or vocal cord paresis.
- Do verify adequate vagus nerve exposure of at least 1.2 in (3 cm) prior to Pod placement. If you do not, it may result in adverse effects such as hoarseness or vocal cord paresis.
- Do verify that the Implant and Pod are placed freely on the vagus nerve with no entrapped branches. If you do not, it may result in adverse effects such as hoarseness or vocal cord paresis.
- Do not re-use the Implant or Pod with another patient. If you do, it will not be sterile.
- Adhere to local e-waste regulations when disposing of any part of the SetPoint System. If you do not, environmental contamination with hazardous substances can result.

Medical Imaging Warnings

There are various types of medical imaging technologies in common use. Although X-rays, computed tomography (CT), ultrasound imaging (sonography), positron emission tomography (PET) are all safe to perform after the patient receives their Implant, it is vital that they always show their Patient ID Card to any healthcare professionals performing these procedures. Specifically for magnetic resonance imaging (MRI), the patient must wait a minimum of two weeks after implantation before they are permitted to have an MRI scan. However, all MRI scans performed more than 14 days after implantation must meet the conditions outlined in the **SetPoint System Magnetic Resonance Imaging (MRI) Safety Information Manual**. **This means that, as long as the patient is implanted, they must inform MRI personnel that the Implant is *MR Conditional*.**

Figure 7 - MR Conditional

⚠ **Warning: The SetPoint Charger and SetPoint Docking Station should never be brought near MRI machines because they are not safe for use in that environment. Thus, the Charger and Docking Station are referred to as MR Unsafe.**

Figure 8 - MR Unsafe

Medical Procedure Warnings

Instruct the patient to use caution with any medical procedure that introduces electrical current, electromagnetic radiation, or thermal energy into tissues in the neck area. The Implant may absorb, intensify, or reflect these energy sources, resulting in localized heating that could damage the device or nearby nerves and vascular structures. This damage may result in pain or discomfort, loss of vocal cord function, or possibly even life-threatening injury if there is damage to a blood vessel. Note that these risks are present whether the Implant is active or suspended. It is extremely important that they always show their Patient ID Card to any healthcare professional performing these procedures so that they can carefully evaluate potential risks due to interactions between the procedure and the SetPoint System. Before proceeding with any procedure that delivers energy to the tissues surrounding the Implant, the healthcare professional should consider alternatives that avoid energy transfer. Specific examples of higher risk procedures around the implantation site that need to be avoided because they could damage the Implant, cause it to malfunction, and/or result in harm including severe injury include:

⚠ **Warning:** Shortwave diathermy, microwave diathermy, ultrasound diathermy or other procedures that induce heat in internal tissues. This does not include diagnostic ultrasound which is permitted.

⚠ **Warning:** Electrosurgery/electrocautery, and ablative surgical techniques that utilize any form of electromagnetic radiation or electrical current to cut, coagulate, or thermally destroy tissues. **For**

electrocautery, do not use within 2 cm of the Implant[1]; if electrocautery is used within 2 cm of the Implant, the Implant will need to be replaced. If using monopolar electrocautery, place the return pad such that the current path is not across the Implant.

⚠ **Warning:** Transcutaneous electrical nerve stimulation (TENS), electroconvulsive therapy or other procedures that apply electrical current through skin surface electrodes.

⚠ **Warning:** Extracorporeal shock wave lithotripsy or other procedures that use pressure waves or induce mechanical forces to break up internal structures.

⚠ **Warning:** Radiation therapy, including forms of photon beam radiation therapy such as x-rays, gamma rays, proton beam therapy, brachytherapy, stereotactic radiosurgery, cobalt machines, and linear accelerators.

If the patient has had any of the above medical procedures around the implantation site, it is very important that, very soon thereafter, they discuss the procedure with their doctor or rheumatologist managing the SetPoint System in order for them to determine whether verification of Implant functionality is necessary.

Radio Frequency (RF) Warnings

The SetPoint System uses radio-frequency (RF) fields for communication between different parts of the system or when charging the Implant or Charger. These RF fields could disrupt the functioning of similar frequency-utilizing devices.

⚠ **Warning:** Instruct the patient not to use the Charger for charging the Implant near devices sensitive to RF interference, while travelling in vehicles such as cars, trains, boats, airplanes, or during any medical treatments, or in proximity to other medical devices.

⚠ **Warning:** The SetPoint System has not been tested with, and may affect the operation of, other implanted devices, such as cardiac pacemakers and implanted defibrillators. Possible effects include, but are not limited to, sensing problems and inappropriate device responses.

⚠ **Warning:** The RF signals from the Charger could theoretically interfere with or be concentrated by other implanted devices such as neural stimulators or insulin pumps.

The Charger and Docking Station are vulnerable to electromagnetic interference from devices that emit RF fields, like cellphones and security scanners. Portable RF communications equipment (including peripherals such as antenna cables and external antennas), RFID scanners and card readers (including animal identification tag scanners) should be used no closer than 12 inches (30 cm) to any part of the Charger and Docking Station. Otherwise, degradation of the performance of this equipment could result.

⚠ **Warning:** If it is suspected that the Charger or Docking Station are not functioning correctly due to electromagnetic interference, try changing the patient's location, waiting until a later time, or turning off the suspected source of interference if possible. Use of the Charger or Docking Station adjacent to or stacked with other equipment should be avoided because it could result in improper operation. If such

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[1] Safety testing was performed using 3 applications of 25 W bipolar and 30 W monopolar electrocautery each at 1 cm from the Implant. Exceeding this number of applications or power setting near the Implant may increase the risk of nerve injury or device failure.

use is necessary, the Charger and Docking Station should be observed to verify they are operating normally.

⚠ **Warning:** The Charger and Docking Station are intended for use indoors, for example in the home or clinic. They should not be used in environments where the intensity of electromagnetic disturbances is known to be high, such as near high-frequency surgical equipment or radio transmitters. They should also not be used in any environment with a posted FCC Notice, Caution or Warning sign indicating the presence of high-intensity radio frequency (RF) fields that surpass normal public exposure limits. These areas are typically indicated by restricted environment signs like those in **Figure 9**. After receiving the Implant, the patient should not enter these areas without seeking medical guidance first. Exposure to high levels of RF could cause the Implant to malfunction or lead to tissue damage in the vicinity of the device.

Figure 9 - Restricted Environment Signage

Education, Training, and Services

In addition to the information provided in this Surgeon IFU, supplementary training materials including, but not limited to, a training presentation, surgical videos, and a training model are available and can be provided upon request. Additional training, if requested, can be arranged with your local SetPoint Medical representative.

Surgical Procedures

Surgical procedures for the SetPoint System should be performed by a surgeon with expertise in the surgical anatomy of the carotid sheath, its contents, and its surrounding structures, and with experience in safe dissection and manipulation of these structures and of cranial nerves such as the vagus nerve.

Implantation Location

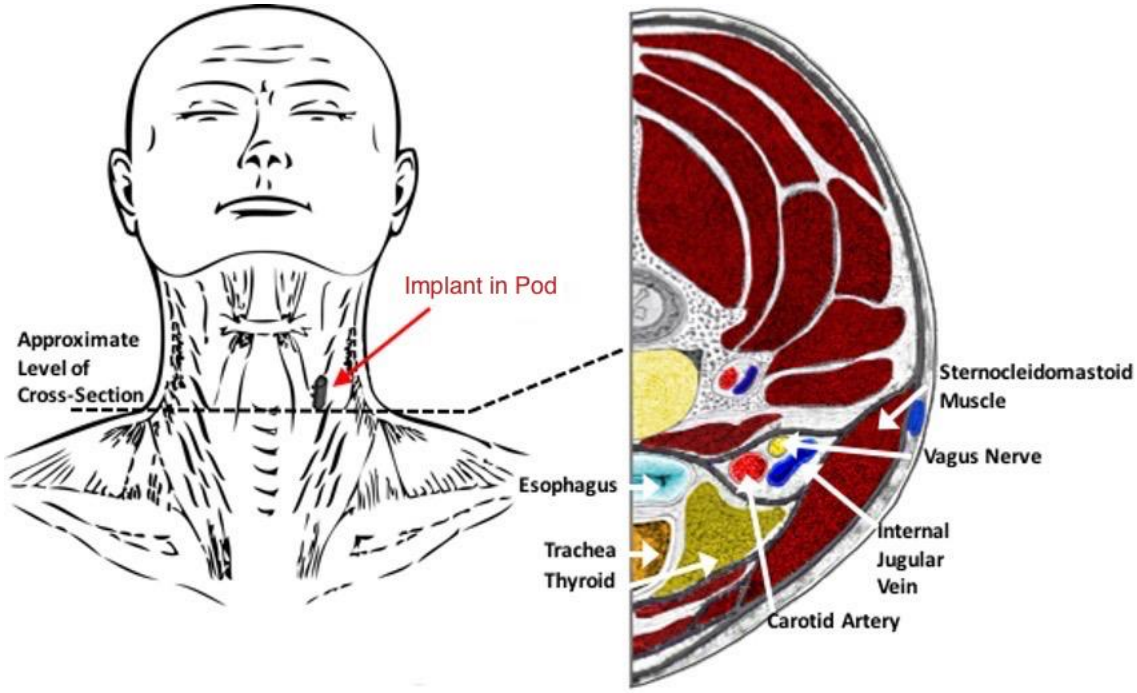

Figure 10 - Implant Location

The Implant must be placed on a segment of the left cervical vagus nerve that is at least 1.2 in (3 cm) long and free from any branches. A suitable segment is typically half-way up between the clavicle and the mastoid process and below both the inferior and superior cervical cardiac branches.

Ideal placement for the Implant to optimize communication with the Charger is between the level of the C4 and C6 cervical vertebrae. The Implant should never be placed below the level of the C7 cervical vertebra. An example placement is illustrated in **Figure 11**.

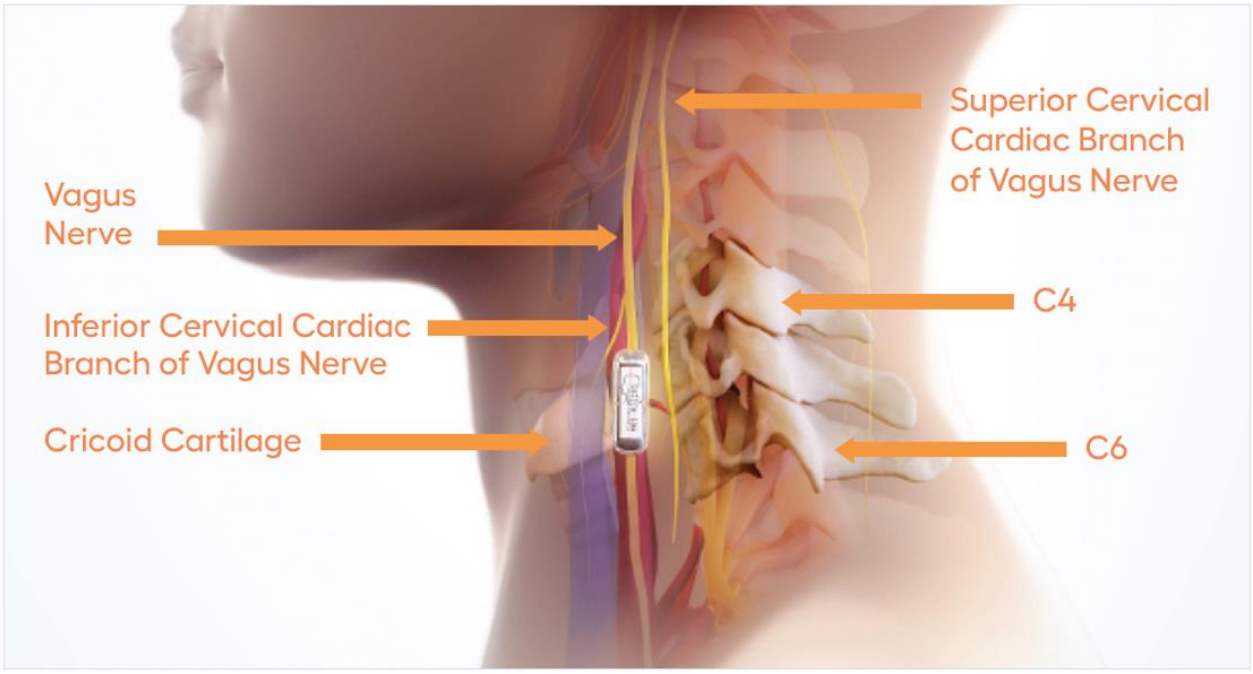

Figure 11 - Relationship Between Implant Implantation Location and Vagus Nerve Branches

Charger Fit Confirmation

To confirm fit of the Charger prior to the implantation procedure, it is recommended that the following steps be performed:

1. Prior to the implant procedure, either place the Charger, or instruct the patient to place the Charger around their neck while they are seated upright.
2. Verify that the magnetic latch closes and remains latched without discomfort.
3. Remove the Charger or instruct the patient to remove the Charger.

Implant Preparation

⚠ **Warning:** Do not use the Implant or Pod if either device shows damage, the packaging shows signs of significant damage, the sterile packaging is breached, the tamper evident label indicates that the package has been opened, or if the product is beyond its expiration date. If you do, you might implant a non-functional device or one with compromised sterility.

1. Carefully open the product box and remove the outer tray. Set aside the Patient ID Card to fill out after the surgery is complete.
2. The outer tray should be opened by pulling the tab on the lid as shown in **Figure 12**. Set aside the outer tray lid and label with the device stickers on it (see **Figure 6** on page 9), to adhere to the Patient ID Card.

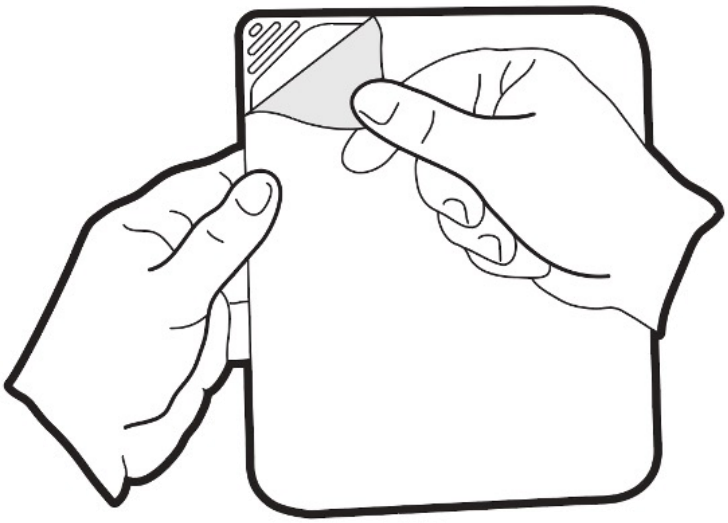

Figure 12 - Opening Tray by Pulling Tab

3. Present the outer tray so that the inner tray can be removed in the sterile field.
4. The inner tray should be opened by pulling the tab on the lid as shown in **Figure 12**.
5. Remove the inner lid and discard (see **Figure 4** on page 7).
6. Place the inner tray on the surgical tray or other sterile surface in the sterile field.
7. If at any point during the surgical procedure the Implant is dropped from a height of over 6 in (15 cm), discard the Implant and utilize the backup.

Implantation

⚠ **Warning:** Do not over-manipulate the vagus nerve throughout the surgical procedure. If you do, it may result in adverse effects such as hoarseness or vocal cord paresis.

Using standard surgical techniques, make a single transverse incision on the left ventral surface of the neck, dissect the fascia and musculature to expose the carotid sheath, and identify the vagus nerve. Then:

1. Locate and expose a segment of the left vagus nerve that is free of branches by circumferentially dissecting the surrounding tissue.

⚠ **Warning:** Do verify adequate vagus nerve exposure of at least 1.2 in (3 cm) prior to Pod placement. If you do not, it may result in adverse effects such as hoarseness or vocal cord paresis.

2. Confirm with a surgical ruler that at least 1.2 in (3 cm) of nerve segment has been exposed to allow for manipulation and insertion of the Pod.
3. If using vessel loops, place under the nerve utilizing standard surgical techniques.
4. Remove a Pod from its plastic holder and discard the plastic holder (see **Figure 4** on page 7).
5. The following are recommended techniques for Pod deployment to accommodate anatomical variations.
    a. Flat Method:
        i. Hold the Pod open facing upwards (see **Figure 13a**) and use forceps to clamp it in the open position along its midline (see **Figure 13b**).
        ii. Insert the Pod under the nerve (see **Figure 13c**) and align it such that the nerve is positioned at the Pod groove (see **Figure 3** on page 7 and **Figure 13d**).

iii. Slowly release the forceps, allowing the Pod to return to its original shape (see **Figure 13e**), closing around the nerve (see **Figure 13f**). If needed, use forceps to gently maneuver the Pod so that nerve is resting in the Pod groove and the Pod opening is facing upwards.

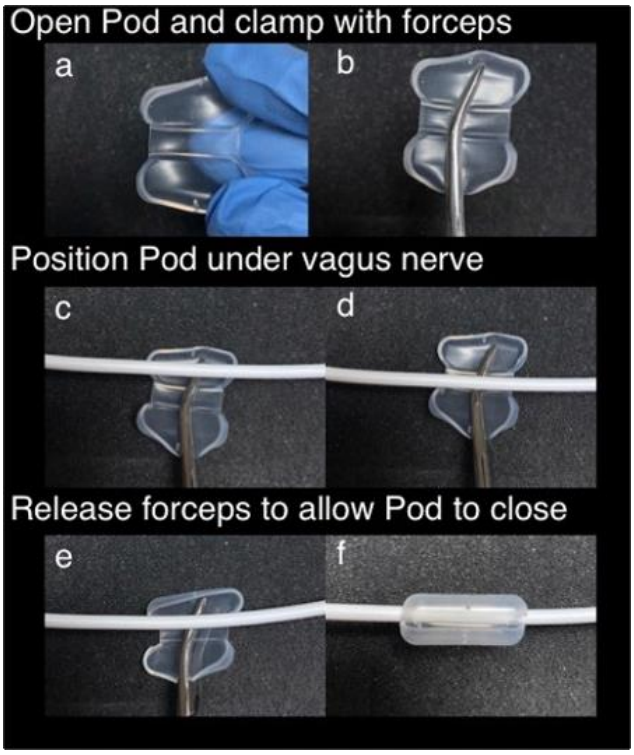

Figure 13 - Pod Implantation: Flat Method

b. Fold Method:
   i. Hold the Pod open facing downwards by pressing on both sides (see **Figure 14a**).
   ii. Fold the Pod off axis (see **Figure 14b**) and use curved forceps to clamp the Pod perpendicular to the Pod groove (see **Figure 3** on page 7 and **Figure 14c**). Turn the forceps so that the Pod opening is facing upwards (see **Figure 14d**).
   iii. Introduce the Pod under the vagus nerve, gently rotating the forceps by approximately 90 degrees to minimize touching the nerve.
   iv. Once the mid-line is positioned under the nerve, rotate the Pod so that the opening is facing upwards (see **Figure 14e**).
   v. Slowly release the forceps, allowing the Pod to return to its original shape (see **Figure 14f** and **Figure 14g**), closing around the nerve (see **Figure 14h**). If needed, use forceps to gently maneuver the Pod so that nerve is resting in the Pod groove and the Pod opening is facing upwards.

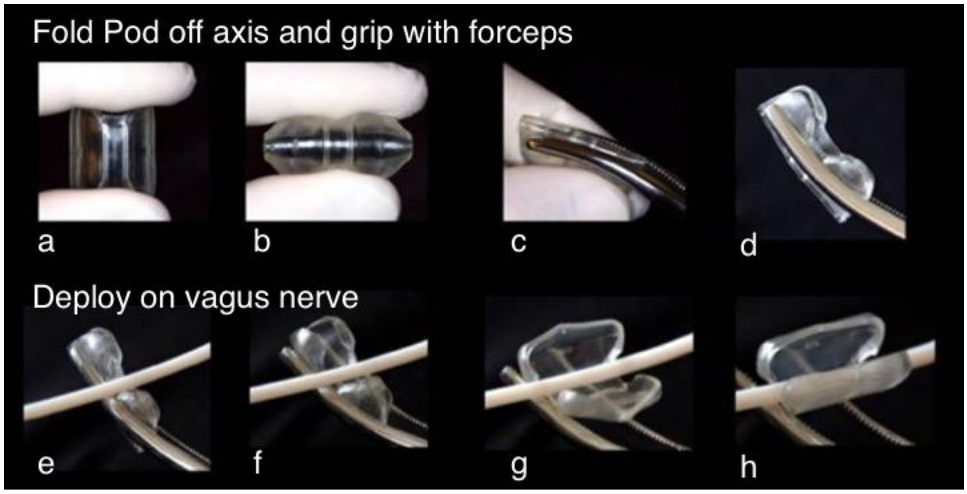

Figure 14 - Pod implantation: Fold Method

6. Insert the Implant into the Pod, (see **Figure 16a-d**) with the head-shaped marking on the Implant oriented rostrally (see **Figure 15**).

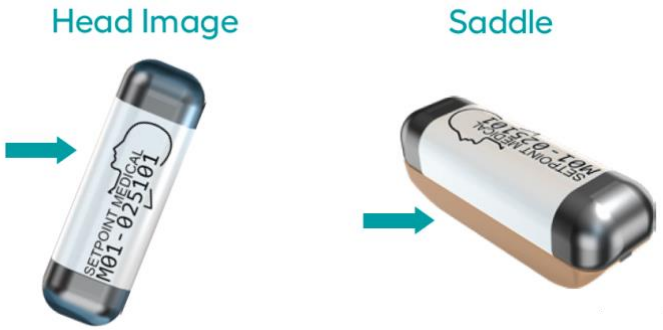

Figure 15 - Head-shaped Marking Indicating Rostral End of the Implant

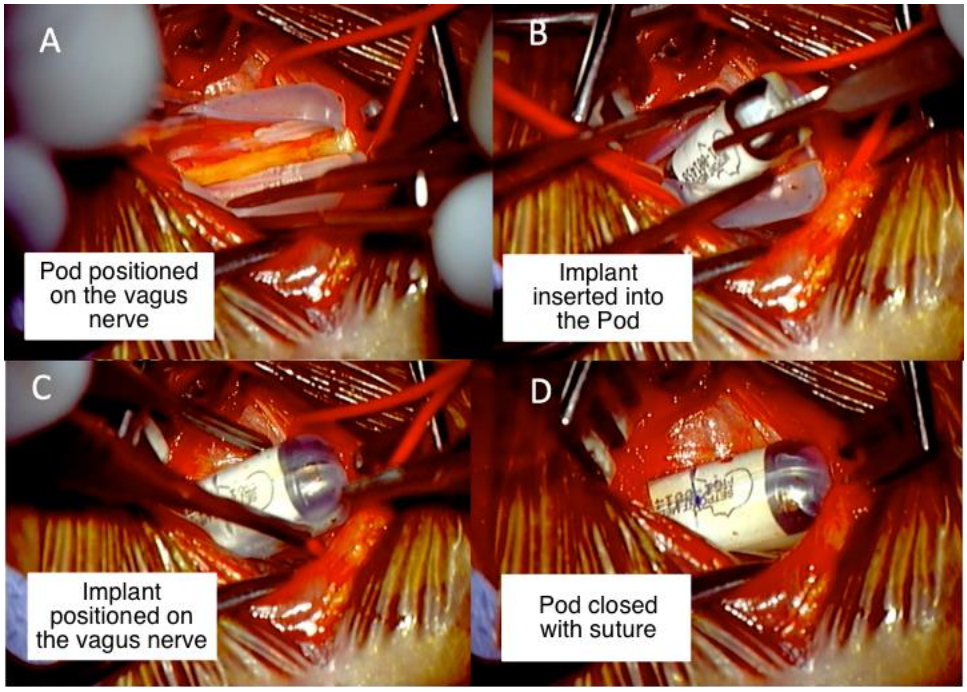

Figure 16 - Pod and Implant Implantation Method

7. Close the Pod around the Implant.
8. While minimizing Pod movement, suture the Pod closed through the suture hole in the Pod (see **Figure 17**) with a non-absorbable 5-0 Prolene suture on a non-cutting needle. Limit the number of throws in the knot to a maximum of four to avoid excessively pulling on the device or nerve.

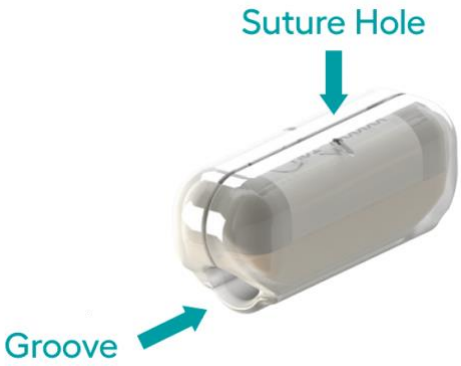

Figure 17 - Pod Suture Hole

⚠ **Warning:** Do verify that the Implant and Pod are placed freely on the vagus nerve with no entrapped branches. If you do not, it may result in adverse effects such as hoarseness or vocal cord paresis.

9. Visualize that the nerve is seated through the ends of the groove of the closed Pod and is in the Implant saddle. Ensure that there are no extra nerve branches or other structures entrapped in the Pod.
10. Verify the closed Pod does not constrict the nerve or vascular tissue by using either a gentle sliding movement of the Pod on the nerve or a slight rotation of the Pod.

Using standard surgical techniques, close the musculature, fascia and skin. Frequent irrigation of the implantation site with generous amounts of bacitracin or equivalent solution can be performed prior to closure for infection control. To minimize scarring, the incision should be closed with cosmetic closure techniques.

Fill out the Patient ID Card and adhere one of the device stickers (see **Figure 18**) onto the correct location on the card (see **Figure 19**). The filled-out card should be provided to the patient after surgery.

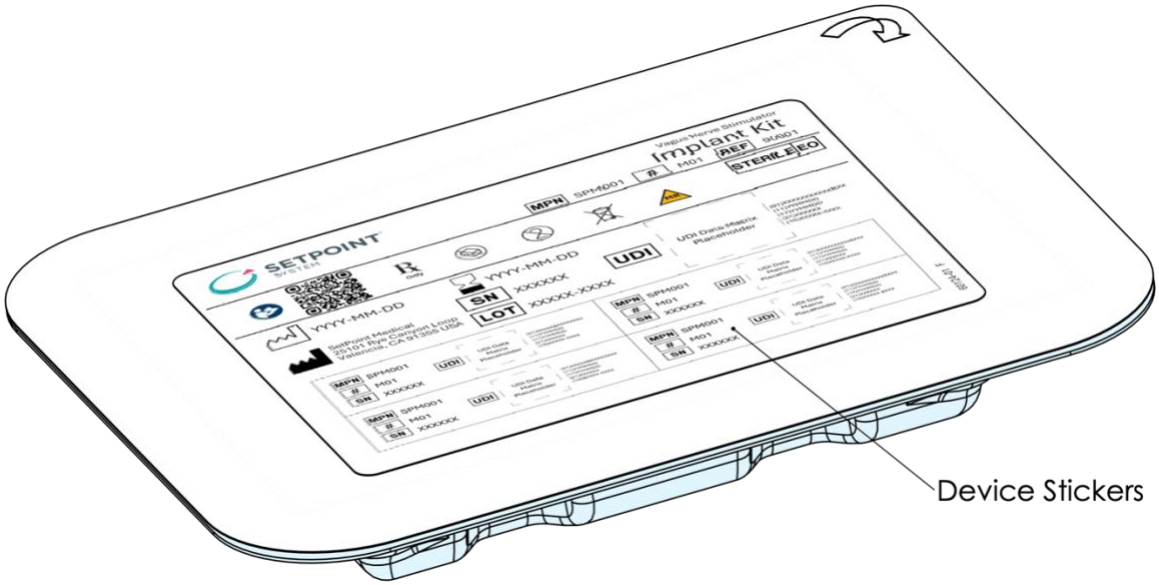

Figure 18 - Device Stickers on Outer Tray Label

Figure 19 - Sample Patient ID Card (Front and Back)

Explantation and Reimplantation

The adverse events associated with explantation or reimplantation are similar to those associated with implantation, but the risk of occurrence of such events is likely to be greater because the presence of scarring around the chronically implanted device makes removal more difficult. If Implant removal is contemplated, SetPoint Medical should be notified prior to explantation or reimplantation surgery.

Therapy programming on the Implant should be suspended, if possible, prior to surgery.

⚠ **Warning:** Do not over-manipulate the vagus nerve throughout the surgical procedure. If you do, it may result in adverse effects such as hoarseness or vocal cord paresis.

If performing a reimplantation, prepare the new Implant as per instructions in section **Implant Preparation**. Using standard surgical techniques, make a single transverse incision on the left ventral surface of the neck, dissect the fascia and musculature to expose the carotid sheath. Then:

1. Expose the Implant in the Pod by incising any tissue capsule surrounding it along the Pod opening (see **Figure 17** on page 19) with the suture visible.
2. Cut the suture and open the Pod.
3. Remove the Implant from the Pod.
4. If performing an explantation, cut the Pod in halves by cutting parallel to the groove in the Pod (see **Figure 17** on page 19) and then remove the halves.
5. If performing a reimplantation, inspect the Pod for damage, specifically the integrity of the suture holes.
    - If the Pod is undamaged, leave it in place, place the new Implant by following steps 6-10 in the **Implantation** section (page 16)
    - If the Pod is damaged, cut the Pod in halves by cutting parallel to the groove in the Pod (see **Figure 17** on page 19) and then remove the halves. Place the new Pod and Implant by following steps 3-10 in the **Implantation** section (page 16).

Using standard surgical techniques, close the musculature, fascia and skin. Frequent irrigation of the incision site with generous amounts of bacitracin or equivalent solution can be performed prior to closure for infection control. To minimize scarring, the incision should be closed with cosmetic closure techniques.

The old Patient ID Card should be retrieved and discarded. If performing a reimplantation, fill out the new Patient ID Card and adhere one of the device stickers (see **Figure 18**) from the new Implant onto the correct location on the card (see **Figure 19**). The new, filled-out card should be provided to the patient after surgery.

⚠ **Warning:** Do not re-use the Implant or Pod with another patient. If you do, it will not be sterile.

⚠ **Warning:** Adhere to local e-waste regulations when disposing of any part of the SetPoint System. If you do not, environmental contamination with hazardous substances can result.

Contact SetPoint Medical to request a return merchandise authorization (RMA) for the explanted Implant and Pod, if removed.

Guidelines for Patient Follow-up

Following the implant procedure, the patient should be cleared for programming of SetPoint System after confirming incision healing, and post-operative recovery. Subsequent follow-up schedule should be determined by the Surgeon based on patient recovery following the implant procedure.

Patient Counseling Information

Patients should be counseled to always carry and present the Patient ID Card to healthcare professionals and providers such as physicians, dentists, imaging technicians (e.g., MRI, X-ray, computerized tomography), physical or occupational therapists, estheticians and beauty-care specialists before pursuing any additional medical, medical imaging or beauty treatments. Failure to present the Patient ID Card may result in a treatment or procedure-related complication and/or may damage the SetPoint System (see sections **Patient Identification (ID) Card** and **Medical Imaging Warnings**). If the patient or

healthcare professional requires the stimulation to be suspended, the patient should **contact the Prescriber's office**.

In case of post-operative concerns or issues, the patient must be counseled to immediately notify the Surgeon for further follow-up.

Appendix A – Explanation of Symbols Used on Packaging and Devices

Symbol	Title	Reference	Description
21 CFR 801.109: Prescription Devices			
	Prescription Only	(b) (1)	Caution: Federal law restricts this device to sale by or on the order of a physician
ASTM F2503			
	Magnetic Resonance (MR) Conditional	Fig. 5	An item with demonstrated safety in the MR environment within defined conditions including conditions for the static magnetic field, the time-varying gradient magnetic fields and the radiofrequency fields
	Magnetic Resonance (MR) Unsafe	Fig. 9	An item which poses unacceptable risks to the patient, medical staff or other persons within the MR environment
WEEE Directive 2012/19/EU			
	Symbol for the marking of EEE	Annex IX	Separate collection for electrical and electronic equipment
IEC 60417			
	Non-ionizing Electromagnetic Radiation	5140	To indicate elevated, potentially dangerous, levels of non-ionizing radiation
	For Indoor Use Only	5957	To identify electrical equipment designed primarily for indoor use
IEC 60529			
IP22	Degree of Protection	N/A	Protected against solid foreign objects of 0.5 in (12.5 mm) Ø and greater; Protection against vertically falling water drops when enclosure is tilted up to 15°.
ISO 15223-1: 5.1. Manufacture			
	Manufacturer	5.1.1	Indicates the medical device manufacturer
	Date of Manufacture	5.1.3	Indicates the date when the medical device was manufactured
	Use-By Date	5.1.4	Indicates the date after which the medical device is not to be used
	Batch Code	5.1.5	Indicates the manufacturer's batch code so that the batch or lot can be identified
	Catalog Number	5.1.6	Indicates the manufacturer's catalog number so that the medical device can be identified
	Serial Number	5.1.7	Indicates the manufacturer's serial number so that a specific medical device can be identified

	Model Number	5.1.10	Indicates the model number or type number of a product
ISO 15223-1: 5.2. Sterility			
	Sterilized Using Ethylene Oxide	5.2.3	Indicates a medical device that has been sterilized using ethylene oxide
	Do Not Use If Package Is Damaged and Consult Instructions for Use	5.2.8	Indicates that a medical device that should not be used if the package has been damaged or opened and that the user should consult the instructions for use for additional information
ISO 15223-1: 5.3. Storage			
	Temperature Limit	5.3.7	Indicates the temperature limits to which the medical device can be safely exposed
	Humidity Limitation	5.3.8	Indicates the range of humidity to which the medical device can be safely exposed
	Atmospheric Pressure Limitation	5.3.9	Indicates the range of atmospheric pressure to which the medical device can be safely exposed
ISO 15223-1: 5.4. Safe Use			
	Do Not Re-Use	5.4.2	Indicates a medical device that is intended for one single use only
ISO 15223-1: 5.7. Others			
	Unique Device Identifier	5.7.10	Indicates a carrier that contains unique device identifier information
ISO 7010			
	Refer to Instruction manual/booklet	M002	To signify that the instruction manual/booklet must be read
	General Warning Sign	W001	To signify a general warning
N/A			
	Manufacturer Part Number	N/A	Indicates the manufacturer part number of a product

Applicable Standards and Regulations

21 CFR 801 Medical Devices – Labeling

ASTM F2503 – 23 Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment

Directive 2012/19/EU of the European Parliament and of the Council of 4 July 2012 on waste electrical and electronic equipment (WEEE)

IEC 60417:2024 Graphical Symbols for use on Equipment

IEC 60529:1989/AMS2:2013/COR1:2019 Degrees of protection provided by enclosures (IP Code)

ISO 15223-1:2021 Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements

ISO 7010:2019 Graphical symbols – Safety colors and safety signs – Registered safety signs

Appendix B – Clinical Studies Summary

The SetPoint System has been evaluated in two U.S. clinical studies with a total of 256 implanted patients. The Pilot study (SPM-008) enrolled 14 multi-drug refractory RA patients to assess the safety and feasibility of implanting the SetPoint System, and the pivotal RESET-RA study (SPM-020) implanted 242 RA patients with inadequate response or intolerance to one (1) or more biological or targeted synthetic DMARDs to evaluate safety and efficacy of the SetPoint System.

At the time of FDA review for the SetPoint System, patients on average had been living with the Implant and receiving stimulation for longer than 1 year, with some patients, those enrolled in the Pilot study, receiving treatment for over 5 years.

This section will focus primarily on the RESET-RA study and will briefly review the Pilot study. Full analysis of the Pilot study is published in Genovese MC, Gaylis NB, Sikes D, et al. Lancet Rheumatology 2020;2(9):e527-e538.

Pilot Study (SPM-008)

Fourteen patients with multi-drug refractory RA underwent implantation with the SetPoint System in a first in human feasibility and safety study. The primary objective of the study was to determine the safety and tolerability of SetPoint System. Secondary endpoints included measurements of standard RA clinical outcomes as well as biomarker analysis of systemic inflammation.

The patients enrolled in the study were randomized to receive daily active stimulation of either 1 min QD (n=6) or 1 min QID (n=4), and non-active (sham) stimulation of 0 min QD (n=4). Efficacy outcomes presented include analysis from QD active and sham stimulation as QID dosing is not indicated for the SetPoint System. Due to the low number of patients in each group, statistically significant differences between groups were not expected, though trends that may indicate efficacy were noted.

There were no device-related adverse events noted during the conduct of the of the Pilot study. Treatment emergent adverse events showed no unusual adverse events during the study other than those related to the device implantation. The implantation procedure was generally well tolerated, and no perioperative infections were observed.

Six clinical adverse events associated with the implantation procedure were observed. All the observed adverse events were similar to observations documented in prior, published studies of other VNS systems or in other common surgical procedures, except for one occurrence of Horner's Syndrome, which resolved without permanent clinically significant sequelae prior to end of study. A separate incident of postoperative left vocal cord paresis occurred in this study, which is an adverse event that has been previously reported in association with vagus nerve surgery. All adverse events resolved over time and there were no permanent, clinically-significant sequalae documented.

There were no adverse, clinically significant changes noted for safety laboratory studies including CBC, electrolytes, renal function and urinalyses. There were no clinically significant changes noted for vital signs and physical examination. Cardiac safety monitoring included 12 lead ECG, rhythm strips collected during delivery of stimulation, and continuous, remote telemetry monitoring. Testing revealed no clinically significant, device associated alterations in the ECG.

Disease activity, as measured by signs and symptoms of Rheumatoid Arthritis, was evaluated using the DAS28-CRP (Disease Activity Score based on 28 joint count and C-reactive protein) as well as CDAI

(Clinical Disease Activity Index). At Week 12, 4 out of 6 patients in the QD group had changes in DAS28-CRP that exceeded the minimal clinically important difference (MCID) of -1.2 and the group mean average change in DAS28-CRP also exceeded -1.2. None of the 4 sham stimulated patients had changes in DAS28-CRP that exceeded the MCID of -1.2. Very similar results were observed when disease activity was scored using the CDAI metric, with the same number of actively stimulated QD patients exceeding the MCID of 12. None of the sham stimulated patients had changes in CDAI that exceeded the MID of -12.

An ex vivo bioassay using lipopolysaccharide (LPS)-elicited cytokine production by monocytes in culture showed that there was a substantial decrease in a subset of proinflammatory cytokines, including IL-1β, IL-6, IL-17, IL-23, and TNF-α, which are known to be relevant in RA pathophysiology at the Week 12 visit compared to Day 0 Visit. These cytokines were reduced in QD stimulated group but not in the sham stimulated group (**Figure 20**).

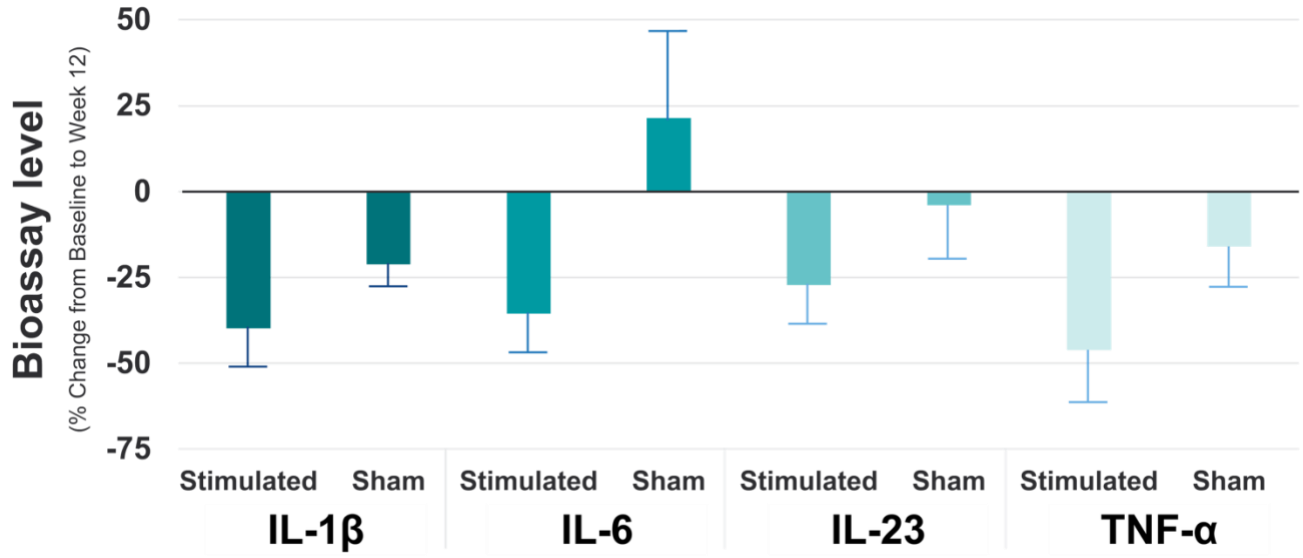

Figure 20 - Percent change from the Day 0 visit in proinflammatory cytokines levels in the TruCulture ex vivo bioassay (mean ± SME)

The primary endpoint of the Pilot study was to assess the overall safety and tolerability of the implantation surgical procedure, the device itself, and the active treatment, and, secondarily, the impact of active stimulation on RA clinical disease activity. Overall, the primary objective of the study was met as the use of the SetPoint System was well tolerated and showed initial clinical and biomarker efficacy in this group of multi-drug refractory RA patients.

RESET-RA Study (SPM-020)

RESET-RA study is a pivotal trial to assess the safety and efficacy of the SetPoint System for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response, loss of response or intolerance to at least one (1) biological or targeted synthetic DMARD (b/tsDMARD). The study enrolled 242 implanted patients across 41 study sites across the United States.

At the time of FDA review, data from the RESET-RA study was available for follow-up visits through Week 48.

Study Design

RESET-RA is a randomized, sham-controlled, double-blind, multicenter, pivotal study with 12-week follow-up for the primary efficacy endpoint, followed by one-way crossover of the control group and a 252-week open-label follow-up of all patients on active stimulation for long-term safety and effectiveness (**Figure 21**).

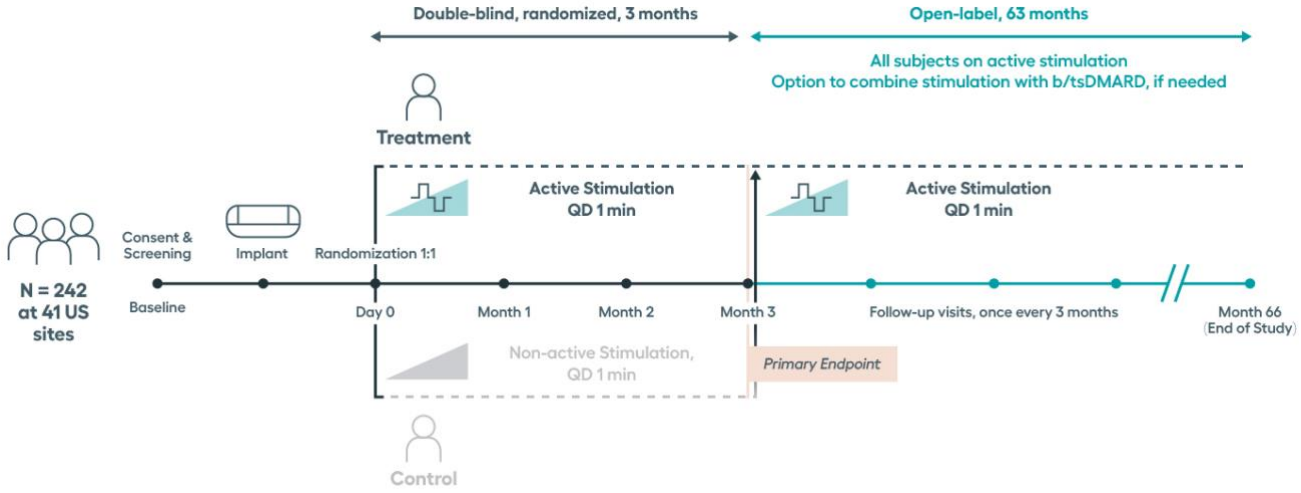

Figure 21 - RESET-RA Study Schematic

Enrollment in the RESET-RA study was limited to patients meeting eligibility criteria.

Key inclusion criteria for participation in RESET-RA included:

- 22-75 years of age at informed consent
- Moderate to severe RA, defined as at least 4/28 tender and 4/28 swollen joints
- Demonstrated inadequate response, loss of response, or intolerance to 1 or more b/tsDMARDs
- Receiving treatment with at least 1 conventional synthetic DMARD for at least 12 weeks and on a continuous non-changing dose and route of administration for at least 4 weeks prior to informed consent and able to continue the same stable dose through Week 12. Missing up to 2 doses due to COVID-19 vaccination was acceptable, except during the 4 weeks preceding informed consent.

Key exclusion criteria included:

- Current, regular use of nicotine-containing products, and lack of agreement to abstain from using nicotine-containing products throughout study participation
- Untreated or poorly controlled psychiatric illness or history of substance abuse
- Significant immunodeficiency due to underlying illness
- History of stroke or transient ischemic attack, or diagnosis of cerebrovascular fibromuscular dysplasia
- Clinically significant cardiovascular disease
- Neurological syndromes, including multiple sclerosis, Alzheimer's disease, or Parkinson's disease
- Uncontrolled fibromyalgia
- History of left or right carotid surgery
- History of unilateral or bilateral vagotomy, partial or complete splenectomy
- Recurrent vasovagal syncope episodes
- Hypersensitivity/allergy to MRI contrast agents and/or unable to perform MRI

All patients were required to remain on a stable background dose of at least 1 conventional synthetic DMARD through the primary endpoint evaluation. All patients were washed off their b/tsDMARDs prior to undergoing implantation procedure and considered enrolled once implantation is completed. Use of b/tsDMARDs from implantation procedure through Week 12 was not allowed. Addition of RA treatment, including adjunctive use of b/tsDMARD in combination with stimulation by SetPoint System, was allowed at any time after completion of Week 12 assessments if the patient experienced worsening of RA symptoms or did not experience adequate clinical improvement.

Demographics

Baseline demographics of patients in RESET-RA study, distributed by treatment and control group, are presented in **Table 3**.

	Treatment (N=122)	Control (N=120)	All (N=242)
Age (years)			
Mean (SD)	55.8 (10.3)	55.5 (10.5)	55.7 (10.4)
Median	57.0	56.5	57.0
Min, Max	25, 75	30, 75	25, 75
Gender			
Male	24 (19.7%)	10 (8.3%)	34 (14.0%)
Female	98 (80.3%)	110 (91.7%)	208 (86.0%)
Ethnicity			
Hispanic or Latino	23 (18.9%)	22 (18.3%)	45 (18.6%)
Not Hispanic or Latino	98 (80.3%)	95 (79.2%)	193 (79.8%)
Not disclosed	1 (0.8%)	3 (2.5%)	4 (1.7%)
Race [1]			
American Indian or Alaska Native	1 (0.8%)	0 (0.0%)	1 (0.4%)
Asian	4 (3.3%)	5 (4.2%)	9 (3.7%)
Black or African American	10 (8.2%)	12 (10.0%)	22 (9.1%)
Native Hawaiian or other Pacific Islander	0 (0.0%)	1 (0.8%)	1 (0.4%)
White	102 (83.6%)	93 (77.5%)	195 (80.6%)
Other	5 (4.1%)	9 (7.5%)	14 (5.8%)
BMI (kg/m^2)			
Mean (SD)	30.7 (7.3)	29.8 (6.7)	30.3 (7.0)
Median	29.6	28.7	29.2
Min, Max	18.9, 56.7	17.9, 54.1	17.9, 56.7
[1] Race reported as "Other" if more than 1 race is selected			

Table 3 - Baseline Demographics of Patients in RESET-RA Study

Medical history of prior biological and targeted synthetic DMARDs (b/tsDMARDs) is presented in **Table 4**.

	Treatment (N=122)	Control (N=120)	All (N=242)
Prior b/tsDMARDs			
Mean (SD)	2.5 (2.0)	2.7 (1.9)	2.6 (1.9)
Median	2.0	2.0	2.0
Min, Max	1.0, 12.0	1.0, 10.0	1.0, 12.0
Number of prior b/tsDMARDs			
0	0	0	0
1	52 (42.6%)	42 (35.0%)	94 (38.8%)

	Treatment (N=122)	Control (N=120)	All (N=242)
2	25 (20.5%)	28 (23.3%)	53 (21.9%)
3 or more (3+)	45 (36.9%)	50 (41.7%)	95 (39.3%)
Prior b/tsDMARD by Classification			
Anti-IL-1 agents	0 (0.0%)	4 (3.3%)	4 (1.7%)
Anti-IL-6 agents	27 (22.1%)	28 (23.3%)	55 (22.7%)
Anti-TNF agents	116 (95.1%)	109 (90.8%)	225 (93.0%)
B-cell depleting agents	13 (10.7%)	21 (17.5%)	34 (14.0%)
JAKi	25 (20.5%)	24 (20.0%)	49 (20.2%)
CTLA4-Ig	32 (26.2%)	36 (30.0%)	68 (28.1%)
Abbreviations: CTLA4-Ig, cytotoxic T-lymphocyte-associated antigen-4 immunoglobulin; IL, interleukin; JAKi, Janus kinase inhibitor; SD, standard deviation; TNF, tumor necrosis factor			

Table 4 - Baseline Prior b/tsDMARD History

Table 5 highlights the baseline disease characteristics, including components for various effectiveness outcomes such as ACR response rate, DAS28-CRP and CDAI at baseline.

	Treatment (N=122)	Control (N=120)	All (N=242)
RA duration (years)			
Mean (SD)	13.0 (10.6)	11.8 (10.4)	12.4 (10.5)
Median	10.0	8.5	9.2
Min, Max	0.1, 55.5	0.7, 51.8	0.1, 55.5
CDAI score			
Mean (SD)	36.1 (12.6)	38.2 (12.8)	37.1 (12.7)
Median	33.8	37.1	35.1
Min, Max	13.5, 73.5	16.5, 74.0	13.5, 74.0
DAS28-CRP score			
Mean (SD)	5.3 (0.91)	5.4 (0.96)	5.3 (0.93)
Median	5.2	5.3	5.3
Min, Max	3.4, 7.6	3.0, 7.9	3.0, 7.9
Serology			
Negative	56 (45.9%)	54 (45.0%)	110 (45.5%)
Positive	62 (50.8%)	66 (55.0%)	128 (52.9%)
Not Done	4 (3.3%)	0 (0.0%)	4 (1.7%)
TJC28			
Mean (SD)	14.1 (6.9)	15.0 (7.3)	14.6 (7.1)
Median	12.4	14.0	14.0
Min, Max	4.0, 28.0	4.0, 28.0	4.0, 28.0
SJC28			
Mean (SD)	9.6 (5.5)	10.5 (5.0)	10.0 (5.2)
Median	7.8	9.2	9.0
Min, Max	4.0, 28.0	4.0, 28.0	4.0, 28.0
HAQ-DI score			
Mean (SD)	1.4 (0.6)	1.3 (0.6)	1.4 (0.6)
Median	1.4	1.4	1.4
Min, Max	0.1, 2.8	0.0, 2.9	0.0, 2.9
Pain (per patient report)			
Mean (SD)	5.5 (2.0)	5.7 (2.2)	5.6 (2.1)

	Treatment (N=122)	Control (N=120)	All (N=242)
Median	5.5	6.0	6.0
Min, Max	1.0, 10.0	1.0, 10.0	1.0, 10.0
Patient Global Assessment			
Mean (SD)	6.2 (2.1)	6.0 (2.3)	6.1 (2.2)
Median	6.0	6.0	6.0
Min, Max	2.0, 10.0	1.0, 10.0	1.0, 10.0
Physician Global Assessment			
Mean (SD)	6.3 (1.9)	6.7 (1.7)	6.5 (1.8)
Median	6.3	7.0	7.0
Min, Max	1.5, 10.0	2.0, 10.0	1.5, 10.0
hsCRP (mg/L)			
Mean (SD)	8.41 (12.34)	8.01 (12.76)	8.21 (12.53)
Median	3.87	2.63	3.08
Min, Max	0.15, 69.76	0.09, 85.48	0.09, 85.48

Abbreviations: CDAI, Clinical Disease Activity Index, DAS28-CRP, Disease Activity Score using 28-joint count and C-reactive protein; Serology includes Rheumatoid Factor and/or Anti-citrullinated Protein Antibody (ACPA); TJC28, tender joint count for 28 joints; SJC28, swollen joint count for 28 joints; hsCRP, High-sensitivity C-reactive protein

Table 5 - Baseline Scores for Disease Activity and ACR Response Rate Components

Safety

Summary of safety of the SetPoint System is reported based on adverse events reporting observed during the RESET-RA study. Adverse events reported by the study doctor as related to either the implantation procedure, device or stimulation associated with the SetPoint System are summarized below.

Overall, no patients during the study experienced a life-threatening complication related to the SetPoint System, and no deaths were reported for any cause.

Summary of Adverse Events (AEs) through primary endpoint at Week 12

During the period from Screening through Week 12, non-serious AEs occurred in 13.9% of treatment and 18.3% of control patients. Most were related to the implantation procedure. The overall rate of serious adverse events (SAEs) related to the implantation procedure or SetPoint System was 1.6% based on the safety population. No events resulted in discontinuation of a patient during this period. There were no Unanticipated Adverse Device Effect (UADEs) and no deaths from Screening to Week 12. The serious adverse events related to the implantation procedure or SetPoint System during the period from implantation procedure to Week 12 are summarized in **Table 6**.

MedDRA Preferred Term	Treatment (N=122) n (%)	Control (N=120) n (%)
Patient with AE	3 (2.5%)	1 (0.8%)
Incision site swelling [1]	1 (0.8%)	0
Vocal cord paresis [1]	1 (0.8%)	0
Dysphonia [1]	0	1 (0.8%)
Pharyngeal perforation [2]	1 (0.8%)	0

Given in the table are number of patients, with percentage, experiencing events for each AE category. At each level of summation, patients are counted only once.
[1] Procedure-related, onset prior to randomization: incision site swelling hospitalized for evaluation that ruled out infection (resolved); vocal cord paresis with dysphagia that led to hospitalization (resolved); dysphonia deemed by investigator significant enough to impair daily activities (resolved, mild sequelae).
[2] Occurred during explant procedure, repaired intraoperatively, no hospitalization required (resolved).

Table 6 – Related, Serious AEs from Implantation Procedure to Week 12

Non-serious AEs related to the implantation procedure and/or Implant are summarized in **Table 7**. Overall, AEs related to the procedure occurred in 16% of patients. These AEs were generally mild to moderate in severity and anticipated based on the nature of the surgical intervention.

MedDRA Preferred Term	Treatment (N=122) n (%)	Control (N=120) n (%)
Patient with AE	17 (13.9%)	22 (18.3%)
Vocal cord paresis	5 (4.1%)	6 (5%)
Dysphonia	4 (3.3%)	3 (2.5%)
Cough	1 (0.8%)	0
Diarrhea	1 (0.8%)	0
Dysphagia	1 (0.8%)	2 (1.7%)
Dyspnea	1 (0.8%)	0
Gastrointestinal complication	1 (0.8%)	0
Implant site hypoesthesia	1 (0.8%)	1 (0.8%)
Implant site inflammation	1 (0.8%)	1 (0.8%)
Implant site swelling	1 (0.8%)	2 (1.7%)
Medical device site swelling	1 (0.8%)	0
Migraine	1 (0.8%)	0
Postoperative wound infection	1 (0.8%)	0
Rash	1 (0.8%)	1 (0.8%)
Scar pain	1 (0.8%)	0
Stitch abscess	1 (0.8%)	0
Swelling	1 (0.8%)	0
Swelling of eyelid	1 (0.8%)	1 (0.8%)
Application site rash	0	2 (1.7%)
Eyelid ptosis	0	1 (0.8%)
Headache	0	1 (0.8%)
Implant site erythema	0	1 (0.8%)
Implant site pain	0	2 (1.7%)
Oropharyngeal pain	0	1 (0.8%)
Procedural pain	0	1 (0.8%)
Suture related complication	0	1 (0.8%)
Thrombophlebitis superficial	0	1 (0.8%)

Given in the table are number of patients, with percentage, experiencing events for each AE category. At each level of summation, patients are counted only once.

Table 7 - Non-Serious Procedure or Implant Related AEs from Implant to Week 12

Stimulation therapy was well-tolerated, with all AEs reported as mild or moderate in severity (**Table 8**).

MedDRA Preferred Term	Treatment (N=122) n (%)	Control (N=120) n (%)
Patient with AE	10 (8.2%)	0
Medical device pain	4 (3.3%)	0
Choking sensation	1 (0.8%)	0
Cough	1 (0.8%)	0
Dysgeusia	1 (0.8%)	0
Oropharyngeal pain	1 (0.8%)	0
Procedural nausea	1 (0.8%)	0
Retching	1 (0.8%)	0
Toothache	1 (0.8%)	0
Given in the table are number of patients, with percentage, experiencing events for each AE category. At each level of summation, patients are counted only once.		

Table 8 - Stimulation Related AEs from Randomization to Week 12

There was a single event of contact dermatitis from use of the Charger. This was addressed by the patient eliminating direct contact with the Charger by wearing clothing or other fabric.

Summary of Adverse Events (AEs) in Long-Term Follow-Up

During open-label, long-term follow-up, from Week 12 until the data cut date (March 10, 2025), 5% of patients in the Treatment to Open Label (TOL) population and 4.2% in the Control to Open Label (COL) population experienced an AE related to implantation procedure or SetPoint System. None of these were serious. Most were related to stimulation, and mild or moderate in severity. Two patients discontinued treatment due to non-serious, related-AEs.

There were no related-serious AEs, Unanticipated Adverse Device Effect (UADEs) or deaths reported during Long-Term Follow-up.

There was one instance of non-serious, moderate vocal cord paresis reported after Week 12. This event is classified as related to the implantation procedure. All other AEs that occurred during long-term follow-up were related to stimulation, all were mild or moderate in severity, occurred in 5% of patients overall. (**Table 9**). These AEs were addressed by adjusting strength or time of stimulation.

MedDRA Preferred Term	TOL (N=121) n (%)	COL (N=120) n (%)
Patient with AE	6 (5%)	5 (4.2%)
Poor quality sleep	2 (1.7%)	0 (0%)
Implant site paresthesia	1 (0.8%)	0 (0%)
Medical device discomfort	1 (0.8%)	0 (0%)
*Medical device site discomfort	1 (0.8%)	0 (0%)
(exacerbation of) Trigeminal neuralgia [1]	1 (0.8%)	0 (0%)
Dysphonia	0 (0%)	1 (0.8%)
*Implant site pain	0 (0%)	1 (0.8%)
Muscle spasms	0 (0%)	1 (0.8%)
Presyncope	0 (0%)	1 (0.8%)
Temporomandibular joint syndrome	0 (0%)	1 (0.8%)
Given in the table are number of patients, with percentage, experiencing events for each AE category. At each level of summation, patients are counted only once.		

MedDRA Preferred Term	TOL (N=121) n (%)	COL (N=120) n (%)
*Relationship to implant device was also indicated for these events [1] Exacerbation of neuralgic symptoms of trigeminal neuralgia		

Table 9 - Stimulation Related AEs during Long-Term Follow-up

Explant Summary

At the time of FDA review for the SetPoint System, the Implant was explanted in 14 of the 242 (5.8% patients). The average duration between implantation and explant among the 14 patients was 469 days, ranging from 141 to 1,364 days. No patients were explanted through Week 12 visit, and 1 Implant was explanted between Week 12 and Week 24 visits. The remainder were explanted after the Week 24 visit.

Effectiveness

The primary endpoint of the RESET-RA study was the proportion of patients achieving ACR20 response at Week 12 from baseline at day of informed consent. After Week 12, the study was open label, with one-way crossover of patients in the control group to the treatment group, with efficacy assessments repeated every 12 weeks. Patients were imputed as non-responder if rescued with steroids or b/tsDMARDs or if missing any data at Week 12 and excluded at all other time points.

ACR20 response at Week 12 showed a statistically significant difference between treatment and control groups (p-value=0.0209, 95% CI 0.6 to 23.1) (**Table 10**).

All Patients						
Group	Total	Number	ACR20 Response %	Difference from Control		
				Difference	95% CI for Difference	p-Value*
Treatment	122	43	35.2%	11.8%	0.6, 23.1	0.0209
Control	120	29	24.2%			
*p-value for all patients based on the Cochran-Mantel-Haenszel test accounting for stratification.						

Table 10 - ACR20 Response at Week 12 from Baseline by Intention-to-treat (ITT)

The evolution of ACR20 response rate through Week 48 is presented in **Table 11**. During Open-Label Follow-up, rates are reported as All Completers and Non-Augmented and show ACR20 response rates further improved and appear to be durable.

ACR20 Study Week	Treatment to TOL			Control to COL			All Treated (after crossover)	
	n	% (n)	SE	n	% (n)	SE	n	% (n)
Baseline	122	0.0% (0)	0.00	120	0.0% (0)	0.00	N/A	
0	122	4.1% (5)	0.02	120	10.8% (13)	0.03		
4	115	27.8% (32)	0.04	113	24.8% (28)	0.04		
8	118	33.9% (40)	0.04	113	26.5% (30)	0.04		
12	122	35.2% (43)	0.04	120	24.2% (29)	0.04		
Long-term Follow-up, All completers								
24	119	44.5% (53)	0.05	117	55.6% (65)	0.05	236	50.0% (118)
36	119	47.9% (57)	0.05	115	55.6% (64)	0.05	234	51.7% (121)
48	119	51.3% (61)	0.05	114	54.4% (62)	0.05	233	52.8% (123)
Long-term Follow-up, Non-augmented								
24	96	52.1% (50)	0.05	98	53.1% (52)	0.50	194	52.6% (102)
36	89	51.7% (46)	0.05	87	62.1% (54)	0.05	176	56.8% (100)

48	77	55.8% (43)	0.06	81	59.3% (48)	0.05	158	57.6% (91)

Note: Baseline/screening at time of consent, Day 0 (day of randomization); patient imputed as non-responder if rescued prior to Week 12, regardless of treatment assignment; patient imputed as non-responder if missing at Week 12. Non-augmented represents patients on SetPoint System monotherapy, without addition of b/tsDMARDs or high-dose steroid therapy.

Table 11 - Evolution of ACR20 Response Through Week 48

The benefits of the SetPoint Therapy may improve slowly over the first 24 weeks of treatment, especially among those who have had experience with multiple prior b/tsDMARDs. Long-term results suggest that the effects of SetPoint Therapy are significant and durable across the entire study population.

Although not statistically powered for the secondary endpoints, consistent trends in favor of treatment were seen across secondary endpoints at Week 12, with results further improved or maintained during Open-Label Follow-up reported from Week 24 through Week 48 as All Completers and Non-Augmented (**Table 12)**.

ACR20 Response from Day 0 by ITT – at Week 12					
Group	**n**	**% (n)**	**Difference from Control**		
			Difference	**95% CI for Difference**	**p-Value**
Treatment	122	31.1% (38)	8.0%	-3.1, 19.0	0.0797
Control	120	22.5% (27)			

ACR20 Response from Day 0 – in open label follow up						
Study Week	**TOL**		**COL**		**All Treated**	
	n	**% (n)**	**n**	**% (n)**	**n**	**% (n)**
Long-term Follow-up, All completers						
24	119	43.7% (52)	117	47.9% (56)	236	45.8% (108)
36	119	50.4% (60)	115	52.2% (60)	234	51.3% (120)
48	119	48.7% (58)	114	44.7% (51)	233	46.8% (109)
Long-term Follow-up, Non-augmented						
24	96	46.9% (45)	98	49.0% (48)	194	47.9% (93)
36	89	49.4% (44)	87	57.5% (50)	176	53.4% (94)
48	77	49.3% (38)	81	48.1% (39)	158	48.7% (77)

DAS28-CRP good/moderate EULAR response by ITT – at Week 12					
Group	**n**	**% (n)**	**Difference from Control**		
			Difference	**95% CI for Difference**	**p-Value**
Treatment	122	60.7% (74)	19.5%	7.3, 31.7	0.0048
Control	120	41.7% (50)			

DAS28-CRP good/moderate EULAR response – in open label follow up						
Study Week	**TOL**		**COL**		**All Treated**	
	n	**% (n)**	**n**	**% (n)**	**n**	**% (n)**
Long-term Follow-up, All completers						
24	118	66.1% (78)	117	70.1% (82)	235	68.1% (160)
36	114	73.7% (84)	107	75.7% (81)	221	74.7% (165)
48	117	72.6% (85)	111	76.6% (85)	228	74.6% (170)
Long-term Follow-up, Non-augmented						
24	95	73.7% (70)	98	70.4% (69)	193	72.0% (139)
36	85	75.3% (64)	82	78.0% (64)	167	76.6% (128)
48	75	77.3% (58)	79	77.2% (61)	154	77.3% (119)

DAS28-CRP response (MCID -1.2) by ITT – at Week 12			
Group	**n**	**% (n)**	**Difference from Control**

			Difference	95% CI for Difference	p-Value
Treatment	122	45.1% (55)	13.2%	1.1, 25.3	0.0528
Control	120	32.5% (39)			

DAS28-CRP response (MCID -1.2) – in open label follow up						
Study Week	TOL		COL		All Treated	
	n	% (n)	n	% (n)	n	% (n)
Long-term Follow-up, All completers						
24	118	53.4% (63)	117	59.8% (70)	235	56.6% (133)
36	114	58.8% (67)	107	62.6% (67)	221	60.6% (134)
48	117	62.4% (73)	111	60.4% (67)	228	61.4% (140)
Long-term Follow-up, Non-augmented						
24	95	60.0% (57)	98	62.2% (61)	193	61.1% (118)
36	85	61.2% (52)	82	64.6% (53)	167	62.9% (105)
48	75	66.7% (50)	79	63.3% (50)	154	64.9% (100)

HAQ-DI Response (MCID ≤ -0.22) by ITT – at Week 12					
Group	n	% (n)	Difference from Control		
			Difference	95% CI for Difference	p-Value
Treatment	122	45.9% (56)	9.0%	-3.3, 21.4	0.0797
Control	120	36.7% (44)			

HAQ-DI Response (MCID ≤ -0.22) – in open label follow up						
Study Week	TOL		COL		All Treated	
	n	% (n)	n	% (n)	n	% (n)
Long-term Follow-up, All completers						
24	119	53.8% (64)	117	61.5% (72)	236	57.6% (136)
36	118	57.6% (68)	115	58.3% (67)	233	57.9% (135)
48	119	55.5% (66)	113	59.3% (67)	232	57.3% (133)
Long-term Follow-up, Non-augmented						
24	96	58.3% (56)	98	63.3% (62)	194	60.8% (118)
36	89	59.5% (53)	87	58.6% (51)	176	59.1% (104)
48	77	53.2% (41)	80	61.2% (49)	157	57.3% (90)

Table 12 - Secondary Efficacy Endpoints at Week 12 and Through Week 48

Table 13 and **Table 14** present mean changes in tender and swollen joint counts from baseline of 14.6 tender joints, and 10 swollen joints (based on 28 joint count) through Week 48.

TJC Study Week	Treatment to TOL			Control to COL			All Treated (after crossover)		
	n	Mean Change From Baseline	SD	n	Mean Change From Baseline	SD	n	Mean Change From Baseline	SD
0	122	-0.4	6.14	120	-1.2	6.47	N/A		
4	116	-5.3	7.38	113	-3.5	8.35			
8	118	-6.1	7.54	113	-3.9	7.85			
12	116	-6.3	8.15	114	-4.3	9.2			
Long-term Follow-up, All completers									
24	119	-7.4	7.63	117	-7.9	9.26	236	-7.6	8.46
36	118	-7.6	7.99	114	-8.8	8.98	232	-8.2	8.50
48	119	-7.9	8.28	114	-8.0	9.12	233	-7.9	8.70
Long-term Follow-up, Non-augmented									
24	96	-8.2	7.75	98	-8.1	9.42	194	-8.14	8.61
36	88	-7.4	7.62	87	-9.9	8.94	175	-8.6	8.37
48	77	-8.3	7.82	80	-9.0	9.24	157	-8.7	8.55

Table 13 - Mean Change in Tender Joint Count for 28 Joints (TJC28) From Baseline Through Week 48

SJC Study Week	Treatment to TOL			Control to COL			All Treated (after crossover)		
	n	Mean Change From Baseline	SD	n	Mean Change From Baseline	SD	n	Mean Change From Baseline	SD
0	122	-0.7	4.53	120	-1.0	4.86	N/A		
4	116	-3.8	5.46	113	-2.8	5.8			
8	118	-4.7	5.79	113	-3.2	5.53			
12	116	-4.4	5.99	114	-3.3	5.59			
Long-term Follow-up, All completers									
24	119	-5.4	6.35	117	-5.7	5.93	236	-5.5	6.14
36	118	-5.7	6.03	114	-6.3	6.27	232	-6.0	6.14
48	119	-5.2	7.07	114	-6.5	5.88	233	-5.8	6.53
Long-term Follow-up, Non-augmented									
24	96	-5.7	6.23	98	-5.5	5.82	194	-5.6	6.02
36	88	-5.6	5.31	87	-6.7	6.19	175	-6.1	5.77
48	77	-5.9	6.14	80	-6.7	5.76	157	-6.3	5.94

Table 14 - Mean Change in Swollen Joint Count For 28 Joints (SJC28) From Baseline Through Week 48

The evolution of proportion of patients with CDAI<10 and DAS28-CRP<3.2, representing patients in low disease activity (LDA) or remission, from randomization through Week 48 is presented in **Table 15** and **Table 16**, respectively.

CDAI < 10 Study Week	Treatment to TOL			Control to COL			All Treated (after crossover)	
	n	% (n)	SE	n	% (n)	SE	n	% (n)
0	122	0.8% (1)	0.01	120	4.2% (5)	0.02	N/A	
4	115	18.3% (21)	0.04	113	8.0% (9)	0.03		

CDAI < 10 Study Week	Treatment to TOL			Control to COL			All Treated (after crossover)	
	n	% (n)	SE	n	% (n)	SE	n	% (n)
8	118	19.5% (23)	0.04	113	11.5% (13)	0.03		
12	120	23.3% (28)	0.04	119	16.0% (19)	0.03		
Long-term Follow-up, All completers								
24	119	27.7% (33)	0.04	117	30.8% (36)	0.04	236	29.2% (69)
36	117	33.3% (39)	0.04	114	35.1% (40)	0.04	231	34.2% (79)
48	118	39.8% (47)	0.05	114	36.0% (41)	0.04	232	37.9% (88)
Long-term Follow-up, Non-augmented								
24	96	34.4% (33)	0.05	98	31.6% (31)	0.05	194	33.0% (64)
36	87	39.1% (34)	0.05	87	40.2% (35)	0.05	174	39.7% (69)
48	76	47.4% (36)	0.06	81	40.7% (33)	0.05	157	43.9% (69)

Table 15 - Evolution of CDAI LDA or Remission Rates Through Week 48

DAS28-CRP ≤3.2 Study Week	Treatment to TOL			Control to COL			All Treated (after crossover)	
	n	% (n)	SE	n	% (n)	SE	n	% (n)
0	122	1.6% (2)	0.01	117	4.3% (5)	0.02	N/A	
4	115	16.5% (19)	0.03	113	8.0% (9)	0.03		
8	117	17.9% (21)	0.04	113	10.6% (12)	0.03		
12	119	26.1% (31)	0.04	119	15.4% (18)	0.03		
Long-term Follow-up, All completers								
24	118	30.5% (36)	0.05	117	31.6% (37)	0.05	235	31.1% (73)
36	114	33.3% (38)	0.04	107	37.4% (40)	0.05	221	35.3% (78)
48	117	42.7% (50)	0.05	111	37.8% (42)	0.05	228	40.3% (92)
Long-term Follow-up, Non-augmented								
24	95	36.8% (35)	0.05	98	32.6% (32)	0.05	193	34.7% (67)
36	85	36.5% (31)	0.05	82	42.7% (35)	0.05	167	39.5% (66)
48	75	49.3% (37)	0.06	79	40.5% (32)	0.06	154	44.8% (69)

Table 16 - Evolution of DAS28-CRP LDA or Remission Rates Through Week 48

The Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) is validated for hand-MRI. RAMRIS measures of inflammation and structural damage also correlate independently with physical function, pain and patient global assessments, with improvements in synovitis and bone erosion associated with improvements in patient reported outcomes. Early MRI erosion progression at 12 weeks is a sensitive predictor of structural damage at 1 year. MRI erosion progression (change > 0.5 in RAMRIS erosion score) by Week 12 is associated with higher disability at 2 years (HAQ), mirroring characteristics of those with 1-year x-ray progression (Ann Rheum Dis. 2017;76(6):992-997; Ann Rheum Dis. 2014;73(11):1968-1974).

In the ITT population, 216 patients had RAMRIS scores measured at baseline and Week 12 (treatment 109, control 107). Prespecified subgroup analyses included patients with an Erosive Phenotype (treatment 57, control 48), defined as synovitis score of 2 or more on any individual joint, at least 4 joints with a score of 1, or any joint with osteitis at baseline, as well as those that had failed only 1 prior b/tsDMARD (46 treatment, 36 control).

The of proportion of bone erosion progressors by all patients and the subgroups of Erosive Phenotype and 1 prior b/tsDMARD are shown in **Table 17**.

Subgroup	n	Treatment % (n)	SE	n	Control % (n)	SE	p-value
All	108	16.7% (18)	0.04	105	20.0% (21)	0.04	0.2476
Erosive Phenotype	53	18.9% (10)	0.05	45	37.8% (17)	0.07	0.0156
1 b/tsDMARD	46	6.5% (3)	0.04	36	25% (9)	0.07	0.0099

Table 17 - Proportion of Bone Erosion Progressors (>0.05 Change in Erosion Score) from Baseline to Week 12 in All Patients and Subgroup of Erosive Phenotype

The mean score changes in bone erosion, synovitis and osteitis from baseline to Week 12 among all patients, patients and the subgroups is presented in **Table 18**.

Mean Change in Erosion Score at Week 12									
Subgroup	**n**	**Treatment**	**SD**	**SE**	**n**	**Control**	**SD**	**SE**	**p-value**
All	108	0.2	0.85	0.08	105	0.5	1.74	0.17	0.0618
Erosive Phenotype	53	0.3	1.09	0.15	45	1.1	2.51	0.37	0.0156
1 b/tsDMARD	46	0.0	0.60	0.09	36	0.8	2.57	0.43	0.0441
Mean Change in Synovitis Scores at Week 12									
Subgroup	**n**	**Treatment**	**SD**	**SE**	**n**	**Control**	**SD**	**SE**	**p-value**
All	108	0.0	1.64	0.16	105	0.1	1.51	0.15	0.2871
Erosive	53	-0.1	2.27	0.31	45	0.0	1.77	0.26	0.4345
1 b/tsDMARD	46	0.1	0.81	0.12	36	0.6	1.78	0.30	0.0900
Mean Change in Osteitis Scores at Week 12									
Subgroup	**n**	**Treatment**	**SD**	**SE**	**n**	**Control**	**SD**	**SE**	**p-value**
All	108	0.1	2.61	0.25	104	0.8	4.13	0.40	0.0662
Erosive	53	0.2	3.74	0.51	45	1.8	6.18	0.92	0.0450
1 b/tsDMARD	46	-0.3	2.22	0.31	36	1.1	4.92	0.82	0.0350

Table 18 - Mean Change in Erosion, Synovitis and Osteitis Scores at Week 12

Continuation of treatment with the SetPoint System was assessed at Week 24, 36 and 48 to evaluate Therapy Persistence. Therapy Persistence on stimulation therapy, and Therapy Persistence on Setpoint System alone (non-augmented) are summarized in **Table 19**.

Persistence	Week 24			Week 36			Week 48		
	Treatment (N=122) % (n)	Control (N=120) % (n)	All (N=242) % (n)	Treatment (N=122) % (n)	Control (N=120) % (n)	All (N=242) % (n)	Treatment (N=122) % (n)	Control (N=120) % (n)	All (N=242) % (n)
Yes: SetPoint as standalone therapy *(no augmentation)*	78.7% (96)	82.5% (99)	80.6% (195)	73.0% (89)	73.3% (88)	73.1% (177)	63.1% (77)	67.5% (81)	65.3% (158)
Yes: Augmentation *(SetPoint with b/tsDMARD additional csDMARD and/or steroid added after Week 12)*	19.7% (24)	15.8% (19)	17.8% (43)	25.4% (31)	23.3% (28)	24.4% (59)	35.2% (43)	29.2% (35)	32.2% (78)

Persistence	Week 24			Week 36			Week 48		
	Treatment (N=122) % (n)	Control (N=120) % (n)	All (N=242) % (n)	Treatment (N=122) % (n)	Control (N=120) % (n)	All (N=242) % (n)	Treatment (N=122) % (n)	Control (N=120) % (n)	All (N=242) % (n)
Augmentation with b/tsDMARD	13.9% (17)	10.0% (12)	12.0% (29)	20.5% (25)	18.3% (22)	19.4% (47)	26.2% (32)	23.3% (28)	24.8% (60)
Augmentation with additional csDMARD and/or steroid	7.4% (9)	6.7% (8)	7.0% (17)	5.7% (7)	7.5% (9)	6.6% (16)	13.1% (16)	10.0% (12)	11.6% (28)
Yes: SetPoint as standalone or augmentation therapy	98.4% (120)	98.3% (118)	98.3% (238)	98.4% (120)	96.7% (116)	97.5% (236)	98.4% (120)	96.7% (116)	97.5% (236)
No: VNS suspended, or device removed	1.6% (2)	1.7% (2)	1.7% (4)	1.6% (2)	3.3% (4)	2.5% (6)	1.6% (2)	3.3% (4)	2.5% (6)

Table 19 - Persistence with SetPoint Therapy (based on ITT)

Patient satisfaction was assessed at Week 24 using five-point Likert rating scale. Additionally, patients were asked a question about whether they would recommend the SetPoint System to family and friends (**Table 20**).

	TOL [1] (N=122)	COL [2] (N=120)	All (N=242)
How satisfied are you with the SetPoint System for treatment of RA?			
N [3]	119	114	233
Somewhat to very satisfied	90 (75.6%)	92 (80.7%)	182 (78.1%)
Neither satisfied nor dissatisfied	14 (11.8%)	12 (10.5%)	26 (11.2%)
Somewhat to very dissatisfied	15 (12.6%)	10 (8.8%)	25 (10.7%)
Would you recommend the SetPoint System to a family member or a friend?			
N [3]	118	114	232
Yes	108 (91.5%)	110 (96.5%)	218 (94.0%)
No	10 (8.5%)	4 (3.5%)	14 (6.0%)

Abbreviations: COL, Control to Open Label; TOL, Treatment to Open Label
[1] Treatment to Open Label (TOL): The TOL population comprises treatment patients from ITT population who received active stimulation through Week 12, completed Week 12 assessments, continued to receive active stimulation during open-label follow-up, and for whom follow-up data are available.
[2] Control to Open Label (COL): The COL population comprises Control patients from ITT population who received non-active (sham) stimulation through Week12, switched to active stimulation after completing Week 12 assessments, continued to receive active stimulation during open-label follow-up, and for whom follow-up data are available.
[3] Percentage calculated based on each analysis population (i.e., TOL, COL).

Table 20 - Patient Satisfaction and Recommendation at Week 24