SETPOINT SYSTEM

PATIENT

INSTRUCTIONS FOR USE

Read all instructions, warnings and cautions carefully.

Failure to do so may damage your 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 Patient Instructions for Use** (Patient IFU), please **contact your doctor or rheumatologist managing the SetPoint System or 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.

PATIENT QUICK REFERENCE GUIDE

SETPOINT SYSTEM USE & CARE

CHARGING CHARGER

- Always place your Charger on the Docking Station when you're not wearing it to keep it fully charged.
- The Charger is fully charged when its LED turns solid green, or when the Docking Station's LED is solid blue.
- Be sure your Charger is fully charged before bringing it to the clinic.

TRAVELING

- Always use the Carrying Case to transport your Charger.
- Do not use your Charger while traveling in any vehicle, including cars, trains, boats, or planes.
- If airport security has questions about your SetPoint System, show them your Patient ID Card.

CLEANING CHARGER

- Clean your Charger with a dry, lint-free cloth, avoiding the magnetic latch.
- To remove lotion or oils, you can use isopropyl alcohol (IPA) wipes–these are also safe for cleaning the magnetic latch area.
- Never spray liquids directly on the Charger or submerge it in any liquid.
- Keep the magnetic latch area free of lint and dirt.

CHARGING IMPLANT

- Wear your Charger around your neck and ensure the magnetic latch is securely closed.
- Charging starts when the LED blinks green or orange, and you hear three beeps that rise in tone.
- Charging is complete when the LED turns solid green and you hear four beeps–three rising tones followed by a repeat of the last tone.
- To stay on track, it's recommended to charge your Implant at the same day and time each week.

Avoid areas marked with radio-frequency (RF) safety warning signs.

Contact your clinic immediately if you experience any pain or discomfort.

Remember to charge your Implant every week

This information is not a substitute for fully reading and understanding the Patient IFU (Instructions for Use). Please refer to the Patient IFU for complete details on how to use the SetPoint System safely and effectively. In addition to reading this guide, please watch the training video here or scan the QR Code.

SETPOINT® SYSTEM

Table of Contents

Introduction

This **SetPoint System Patient Instructions for Use** (Patient IFU) describes how your SetPoint System works and gives you important safety tips for using it. Remember this guide does not replace advice given by your doctor or rheumatologist. You should always talk to your doctor or rheumatologist for individual health needs. You should read and understand this document to ensure that you can use the SetPoint System appropriately.

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

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 a Docking Station (F)
- A Programmer (E)

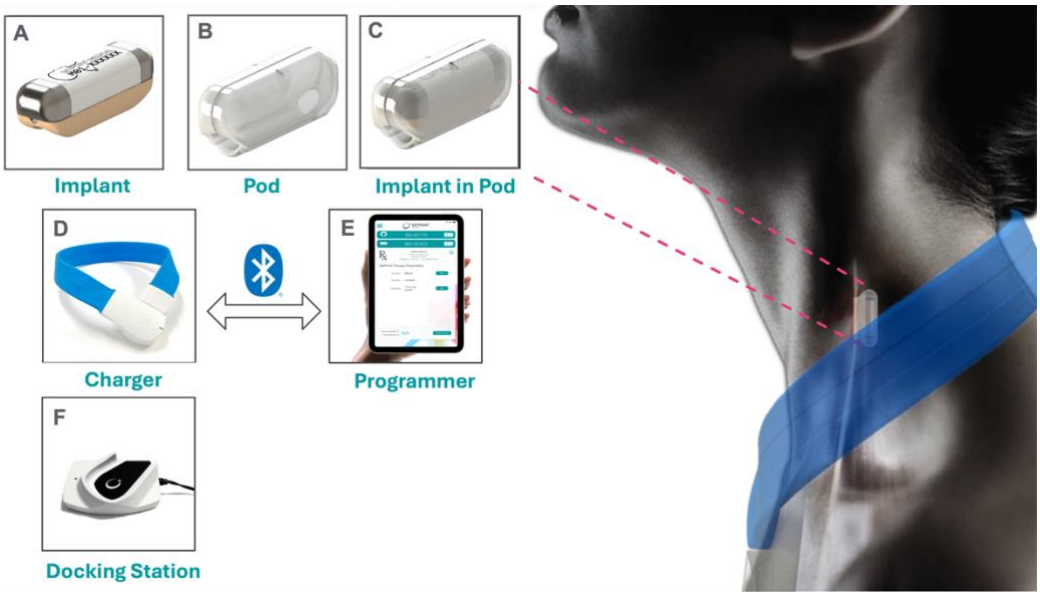


Figure 1 – SetPoint System and Components

Implant and Pod

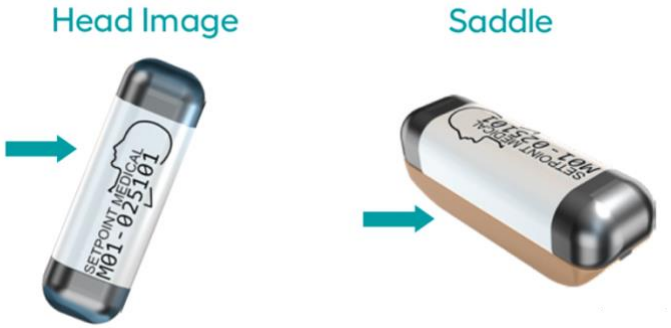


Figure 2 - Implant

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). An experienced surgeon implants the device 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.

Automatic Stimulation

Your doctor or rheumatologist managing the SetPoint System, or a qualified staff member, will program your Implant with the information that describes the strength and timing of stimulation. Once programmed, the Implant uses a built-in timer to deliver therapy at the scheduled time every day.

What to Do if the Stimulation is Uncomfortable

You may or may not feel a sensation while the Implant is stimulating your vagus nerve. If the sensation becomes uncomfortable, you should **contact your doctor or rheumatologist managing the SetPoint System** as soon as possible. Your doctor or rheumatologist managing the SetPoint System may require you to visit the clinic to adjust the programming based on your comfort level.

Suspending Therapy

If you and your doctor or rheumatologist managing the SetPoint System determine it is necessary to temporarily pause receiving doses, visit the clinic to have your automatic treatment suspended or subsequently resumed.

Charger

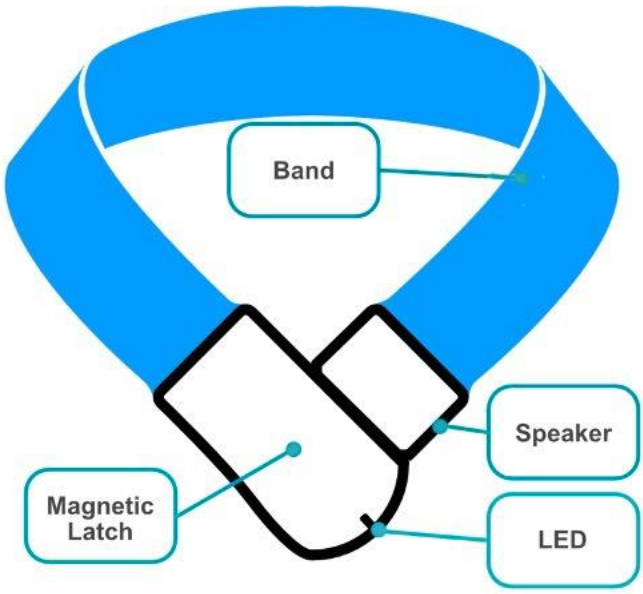


Figure 3 – The Charger

The Charger is a device worn around your neck. It is used for charging your Implant at home and for programming the Implant at the clinic. It is recommended to be worn once a week to charge the Implant.

The Charger is about 24 in (61 cm) long and 1.5 in (3.8 cm) wide, when unlatched and laid flat, and weighs about 9 oz (270 g). The Charger does not have any buttons or switches, but it does have an LED and a speaker.

The Charger only comes in one size that is meant to fit most people, forming a circular ring about 21 in (53 cm) in circumference when latched. Before the implant procedure, your doctor or rheumatologist managing the SetPoint System will perform a fit and tolerability test. This makes sure it fits comfortably around your neck and that the magnetic latch closes.

Docking Station

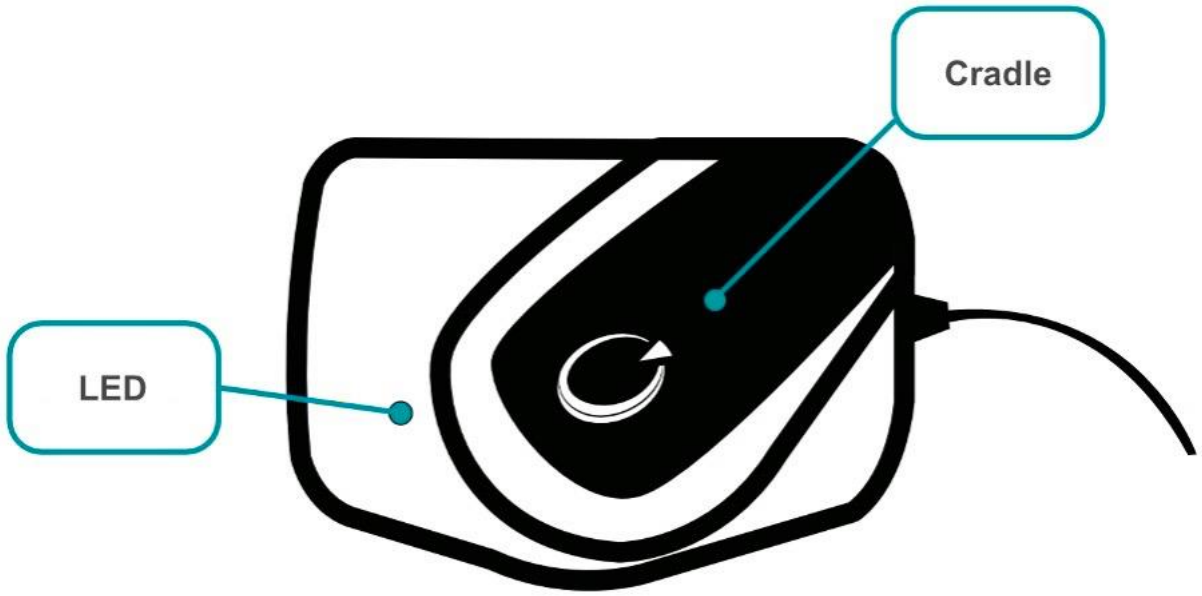


Figure 4 – The Docking Station

The Docking Station is provided with the Charger. The Docking Station is for charging and storing the Charger. Only the Docking Station provided in the Carrying Case should be used to charge the Charger. Use of any other wireless power supply may damage the Charger, the wireless power supply, or both.

The Docking Station is about 4.5 in (11.4 cm) wide, 3 in (7.6 cm) deep, and 2 in (5.0 cm) tall, and weighs about 10 oz (290 g). The Docking Station does not have any buttons or switches, but it does have an LED. The Docking Station has a cradle for placing the Charger on and a power cord that must be plugged into an electrical outlet. The Docking Station cannot be serviced at home. The Docking Station is meant to be used indoors and should always stay plugged in at home.

Programmer

Programmer is an app installed on an Apple iPad® that is only used by a trained healthcare professional. They use it 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.

Patient Identification (ID) Card

The Patient ID Card, shown in **Figure 5**, is completed by your healthcare professional and given to you following surgery. This card serves as proof of an implanted medical device within your body. It is important to always have your 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 your Implant, which is necessary to ensure that any treatments are compatible with it. Always 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. 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 you change your doctor or rheumatologist managing the SetPoint System, or lose your card, **contact SetPoint Medical for a replacement card**.

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

Important Safety Information

Read all instructions, warnings and cautions carefully. If you have any questions consult with your doctor or rheumatologist managing the SetPoint System. If you do not follow these guidelines, the SetPoint System could get damaged and work incorrectly such that your rheumatoid arthritis may be adversely affected.

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).

You should not use the SetPoint System:

- If you have had certain health procedures that would interfere with how the device works, for example,
  - If you have had surgery to remove the vagus nerve (vagotomy).
  - If you have had your spleen removed (splenectomy).
- If your doctor or rheumatologist managing the SetPoint System determines that it might not be safe for you to have the surgery, for example,
  - If you have spine disease in your neck that makes it risky to place a breathing tube (intubate).
  - If you cannot be safely given anesthesia for surgery.
- If you cannot safely use the SetPoint Charger, for example,
  - If your neck is too large to wear the SetPoint Charger.
  - If you have a pacemaker or a defibrillator implanted.

Warnings & Precautions

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

- Before having any diagnostic or treatment procedures, present the Patient ID Card to the healthcare provider, such as a physician, dentist, imaging technician (e.g., MRI, X-ray, computerized tomography), physical or occupational therapist, esthetician, or beauty-care specialist. Neglecting to inform the healthcare provider may result in a treatment or procedure-related complication and/or may damage the SetPoint System (see **Medical Imaging Warnings** below).
- Do not 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 SetPoint Charger while it is covered (e.g., with a scarf or similar material), in direct sunlight, or in air temperatures exceeding 90 °F (32 °C). If you do, it may cause the Charger to rapidly overheat and prematurely shut down.
- Do not continue to use the SetPoint System beyond its expected service life. The Charger and Docking Station each have a 5-year service life. Use after 5 years can lead to additional risks associated with device deterioration over time. Signs of performance degradation include incomplete Implant charging during the weekly session. The Implant has a 10- year service life, after which time it will stop providing daily stimulation, it will no longer recharge, and the Implant will need to be replaced.
- Do not use third-party wireless chargers with the SetPoint Charger or try to charge other devices with the SetPoint Docking Station. Using incompatible accessories with the SetPoint System could lead to device damage or malfunction.
- Do not position the SetPoint Charger around the neck if there are any unhealed wounds. If you do, it increases the risk of infection.

- Do not apply excessive force to the SetPoint Charger or handle it roughly. If you do, it may damage its internal electrical components, potentially causing malfunction.
- Do not use any cleaning product on the SetPoint Charger other than isopropyl alcohol (IPA) wipes. If you do, it could damage the Charger or leave harmful or irritating residues.
- 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.
- Do not modify or tamper with the SetPoint Charger or Docking Station. If you do, it could alter their function or bypass safety features and result in harm.

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 you receive your Implant, it is vital that you always show your Patient ID Card to the healthcare professionals performing these procedures. Specifically for magnetic resonance imaging (MRI), you must wait a minimum of two weeks after implantation before you 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 Implant remains in your body, you must inform MRI personnel that the Implant is *MR Conditional***.

Figure 6 - 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 7 - MR Unsafe

Medical Procedure Warnings

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 while the Implant is stimulating the vagus nerve (one minute per day) and while it is not stimulating the vagus nerve. It is extremely important that you always show your Patient ID Card to any healthcare professional performing these procedures so that they can carefully evaluate potential risk due to interactions between the procedure and the SetPoint System. Before proceeding with any procedure that delivers energy to the tissues surrounding the Implant, they 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.

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

⚠ **Warning:** Extracorporeal (outside the body) shock wave lithotripsy (a medical procedure used to break up kidney stones and other hardened masses into smaller pieces, allowing them to be passed naturally through the urinary tract) 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 you have had any of the above medical procedures around the implantation site, it is very important that very soon thereafter you discuss the procedure with your 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:** Do not 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 your 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 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 8**. After receiving the Implant, do 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 8 - Restricted Environment Signage

Other Help Using Your SetPoint System

In addition to reading this guide, you can watch the training video by clicking this link or scanning the QR Code in **Figure 9** or by looking at the **Patient Quick Reference Guide** for help on how to use your SetPoint System. If you still need more training, you can ask your doctor or rheumatologist managing the SetPoint System.

Figure 9 – Scan to Watch Training Video

Using Your SetPoint System

The table below shows the conditions for transport, storage, and use of the Charger and Docking Station.

Use	Temperature	Humidity	Altitude
Transport: In Carrying Case	50 to 104 °F (10 to 40 °C)	15 to 93 %RH	Up to 98,425 ft (30,000 m)
Storage: Charger on Docking Station			Up to 9,843 ft (3,000 m)
Use: Charging the Implant	50 to 90 °F (10 to 32 °C)		

Table 2 – Transport, Storage, and Use Conditions

⚠ **Warning:** Do not 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.

⚠ **Warning:** Do not use the SetPoint Charger while it is covered (e.g., with a scarf or similar material), in direct sunlight, or in air temperatures exceeding 90 °F (32 °C). If you do, it may cause the Charger to rapidly overheat and prematurely shut down.

The Charger normally heats up during use, potentially reaching up to 118 °F (48 °C). To prevent overheating and premature shutdown, the Charger needs to be at or below 90 °F (32 °C) before being used to charge the Implant. If the Charger has been stored above 90 °F (32 °C), it must be allowed to cool down to this temperature, which can take up to 10 minutes.

⚠ **Warning:** Do not continue to use the SetPoint System beyond its expected service life. The Charger and Docking Station have a 5-year service life. Use after 5 years can lead to additional risks associated with device deterioration over time. Signs of performance degradation include incomplete Implant charging during the weekly session. The Implant has a 10- year service life, after which time it will stop providing daily stimulation, it will no longer recharge, and the Implant will need to be replaced.

The rechargeable battery in the Charger is rated to last for at least 5 years. If you cannot complete the weekly Implant charging session with a fully charged Charger, the entire Charger may need to be replaced as its battery cannot be replaced or serviced at home. **Contact your doctor or rheumatologist managing the SetPoint System** if you believe there are any issues with your Charger.

The rechargeable battery in the Implant is rated to last for 10 years. After this point, the Implant is considered expired. It will need to be replaced because it will no longer deliver daily stimulation, and the battery will no longer charge. The entire Implant will be replaced because the Implant's battery cannot be changed. Your doctor or rheumatologist managing the SetPoint System will be able to determine that it is time to replace the Implant by looking at information provided by the Programmer during a clinic visit. **Contact your doctor or rheumatologist managing the SetPoint System** if you believe there are any issues with your Implant.

Unpacking and Setting Up Your Charger and Docking Station

Your Charger and Docking Station will be provided to you in a Carrying Case. This Carrying Case should be used whenever you are transporting the Charger. When not being transported, your Charger and Docking Station should be unpacked from the Carrying Case, the Docking Station should be plugged into an electrical outlet, and the Charger should be placed on the Docking Station.

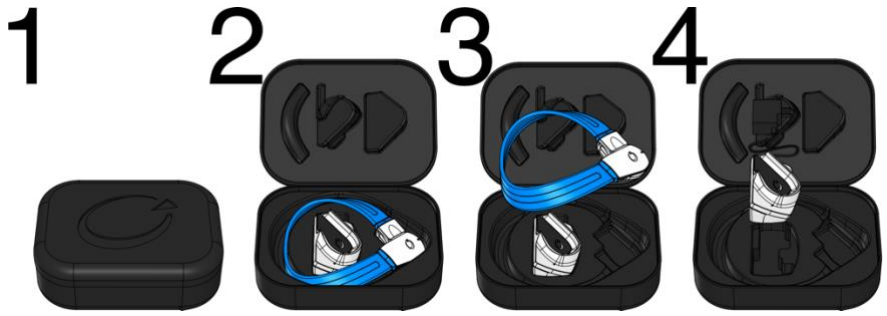


Figure 10 – Unpacking Charger and Docking Station

1. Place your Carrying Case on a flat surface with the logo on top and the handle facing away from you.
2. Unzip the Carrying Case and flip the top open.
3. Remove your Charger from the Carrying Case and set it aside.
4. Remove your Docking Station from the Carrying Case.
5. Uncoil the power cord and plug your Docking Station into an electrical outlet.
6. Place your Docking Station on a flat surface, like a dresser, with enough room to accommodate the Charger once placed on the Docking Station and where you can ensure that the Docking Station is at least 8 in (20 cm) away from you during use.
7. Confirm that your Docking Station has a **solid pink** LED before placing the Charger on the Docking Station. If the LED is not showing a **solid pink** light, see **Appendix D – Troubleshooting**.

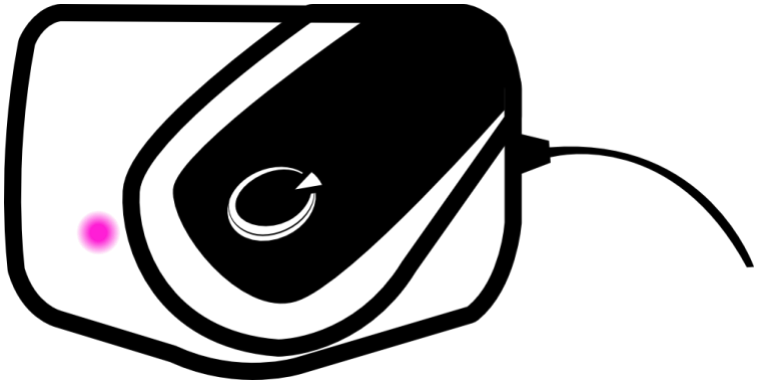


*Figure 11 – The Docking Station shows a **pink** LED when it is plugged in, but not charging the Charger.*

Charging Your Charger

⚠ **Warning:** Do not use third-party wireless chargers with the SetPoint Charger or try to charge other devices with the SetPoint Docking Station. Using incompatible accessories with the SetPoint System could lead to device damage or malfunction.

Your Charger should be placed on the Docking Station whenever it is not being transported or used to charge your Implant (whenever you are not wearing it).

1. Place your Charger on the Docking Station's cradle as shown, making sure that the latch is closed. The Charger must be latched while charging.

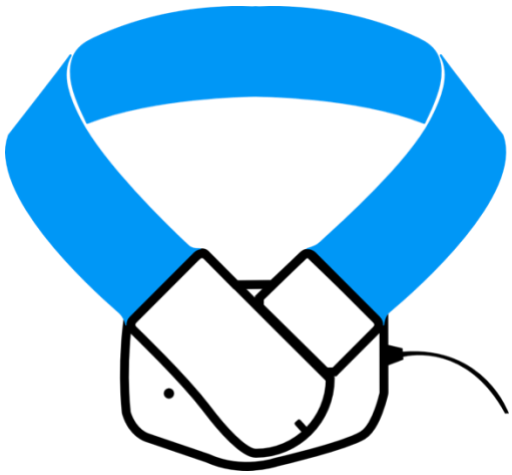


Figure 12 – The Charger must be latched closed when placed on the Docking Station's cradle.

2. The Docking Station's LED will begin **blinking blue** to show that it is charging. Once the Charger is fully charged, the Docking Station's LED will display **solid blue**. If the Docking Station does not show a **blinking** or **solid blue** LED, see **Appendix D – Troubleshooting.**

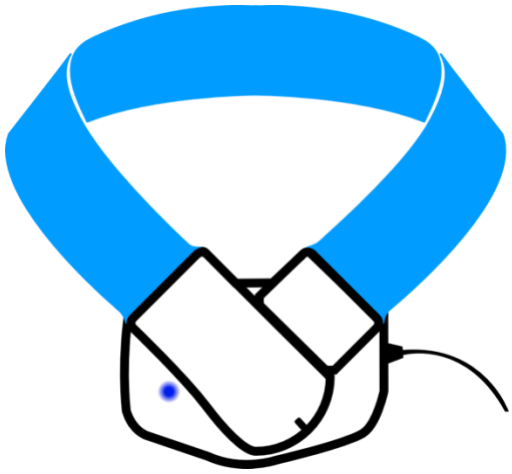


*Figure 13 – The Docking Station's LED **blinks blue** when charging or shows **solid blue** when charging is complete.*

3. While the Charger is placed on the Docking Station's cradle, tapping on the Charger logo will show its battery level. If the Charger's LED shows **solid green**, it is fully charged. If the Charger LED shows **blinking green**, it has enough charge to charge the Implant. If the Charger LED shows **blinking orange**, it is charging but not ready yet to charge the Implant.

Figure 14 – Tapping on the Charger while it is on the Docking Station will show its battery level.

Even if the Charger is done charging, there is no need to take it off the Docking Station. Leaving the Charger on the Docking Station ensures that it is always fully charged.

Before visiting the clinic or charging your Implant, you should make sure that your Charger has a full charge by tapping on the Charger logo while it is on the Docking Station and looking for a **solid green** LED.

Charging Your Implant

SetPoint Medical recommends that you charge your Implant each week using your Charger.

⚠ **Warning:** Do not position the SetPoint Charger around the neck if there are any unhealed wounds. If you do, it increases the risk of infection.

The Charger is only to be placed on skin without cuts or wounds. If the Charger needs to be used on an open wound, the wound should be covered in sterile gauze or bandage first.

For ease of use, the Charger has both an LED and a speaker for showing charge status. If needed, you can use a mirror to look at the Charger LED.

1. Tap on your Charger logo while it is on the Docking Station and look for a **green** LED. If the LED is **orange**, leave the Charger on the Docking Station until it turns **green**.
2. Remove your Charger from the Docking Station.
3. Unlatch your Charger by pulling or twisting the two halves of the magnetic latch apart. Do not touch the pins on the inside of the magnetic latch.
4. Carefully lift your Charger over your head or bring it around your neck. The magnetic latch should rest on the front of your neck with the SetPoint logo half on the right side.
5. Take both halves of the magnetic latch and press them together. The magnets in the Charger should snap into place and latch easily. If the Charger is hard to latch, it is likely twisted or upside down. You might need to use a mirror to see better or ask someone to help if it is tricky.
6. Make sure the latch is securely closed so your Charger will not fall off. Adjust it so it sits comfortably on your neck.

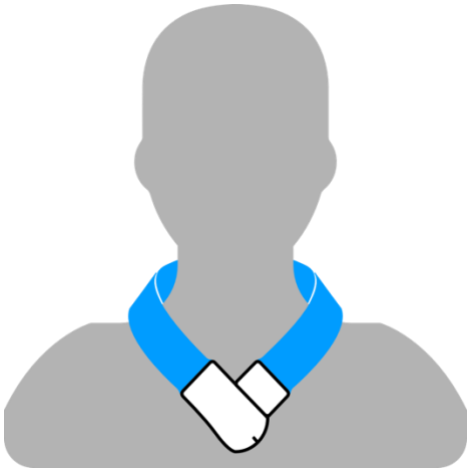


Figure 15 – The Charger should rest comfortably around your neck as shown.

7. The Charger's LED will begin to **slowly pulse white** while it is trying to connect to your Implant. Once it has connected to your Implant, the Charger will play **two beeps that go *up* in tone**. If at any time after connecting it plays **two beeps that go *down* in tone**, it means the Charger has lost connection with your Implant.
8. The Charger will play **three beeps that go *up* in tone** when it begins charging the Implant and will then show an **orange** or **green** LED.
9. It is recommended that you charge your Implant for approximately 5 minutes each week or until the battery is full, whichever comes first. The Charger's LED shows **solid green** and plays **four beeps (three beeps that go *up* in tone and a fourth beep that is a repeat of the last tone)** when your Implant battery is full. After your Implant has reached full charge, the beeps will repeat every 30 seconds until you take your Charger off.
10. Once charging is completed, unlatch your Charger and remove it from your neck.
11. Latch your Charger and place it back on the Docking Station.

Following a Routine

Creating a routine can make it easier to remember when to charge your Charger and Implant. SetPoint Medical recommends the following routines:

1. You should wear your Charger to charge your Implant for about 5 minutes on the same day each week. For example, you may choose to charge your Implant every Sunday morning or right before going to bed every Saturday night. Less frequent charging may require longer time to fully charge the Implant.
2. When you are not wearing your Charger, it should be placed on your Docking Station. This makes sure that the Charger always has a full charge when you need it for charging the Implant or for a clinic visit.

Traveling With and Packing Your Charger and Docking Station

⚠ **Warning:** Do not apply excessive force to the SetPoint Charger or handle it roughly. If you do, it may damage its internal electrical components, potentially causing malfunction.

When at home, it is important to follow the recommended routine outlined above to maintain your devices' batteries. When traveling, you should consult with your doctor or rheumatologist managing the SetPoint

System on what equipment you should take with you depending on the length of your trip. If you need to bring your Charger or Docking Station, always use your Carrying Case.

You should bring your Charger to your rheumatology visit as it may be needed to adjust the programming on your Implant. If you are planning a long trip that requires your Docking Station, bring a standard plug adapter if traveling internationally. Please **contact your doctor or rheumatologist managing the SetPoint System** if any issues arise during travel.

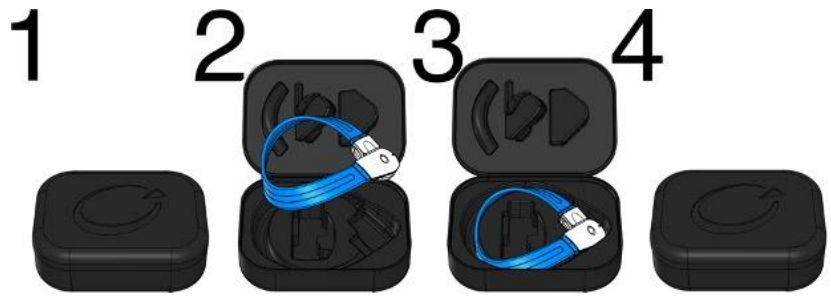


Figure 16 – Packing the Charger in the Carrying Case

1. Place your Carrying Case on a flat surface with the logo on top and the handle facing away.
2. Unzip your Carrying Case and flip the top open.
3. Place your latched Charger in the Carrying Case.
4. Zip your Carrying Case shut.

The Charger cannot be turned off, but it switches to low power mode by itself after about 1 minute of inactivity. Opening or closing the Charger or removing the Charger from the Docking Station will wake it up, and it will begin looking for an Implant.

Pack your Carrying Case in your carry-on luggage when traveling in an airplane. Provide your Patient ID Card to security personnel when going through airport security if they have any questions or concerns about your SetPoint System. See https://www.tsa.gov for more information about traveling with medical equipment.

Cleaning

⚠ **Warning:** Do not use any cleaning product on the SetPoint Charger other than isopropyl alcohol (IPA) wipes. If you do, it could damage the Charger or leave harmful or irritating residues.

- Use a dry, lint-free cloth to clean your Charger avoiding the magnetic latch.
- If needed, use isopropyl alcohol (IPA) wipes to clean lotion and oils off your Charger and to clean the magnetic latch area.
- Never spray your Charger with any substance or put it in any liquid.
- Keep lint and dirt out of your Charger's magnetic latch area.

Replacement and Disposal

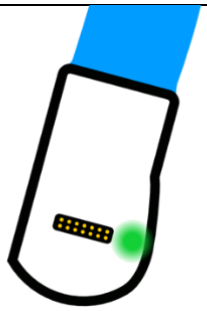
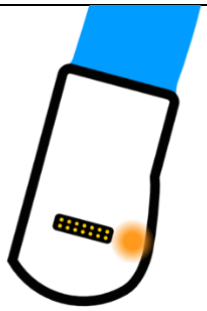
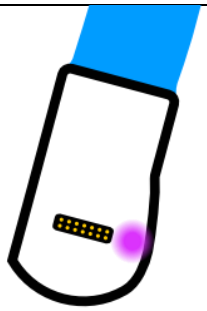
⚠ **Warning:** Adhere to local e-waste regulations when disposing of any part of the SetPoint System. If you do not, environmental contamination with hazardous substances can result.

To reorder the Charger or Docking Station, **contact your doctor or rheumatologist managing the SetPoint System**. You may need to return the old Charger and Docking Station to your doctor or rheumatologist, but if instructed to dispose of it please follow local e-waste regulations.

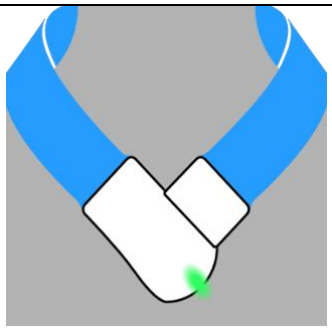
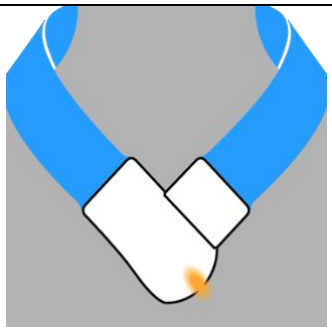
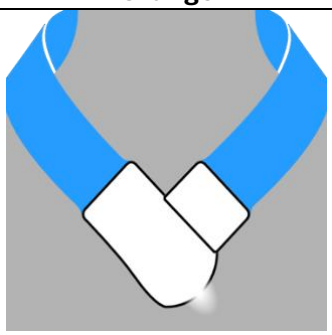
Appendix A - Charger LED Status

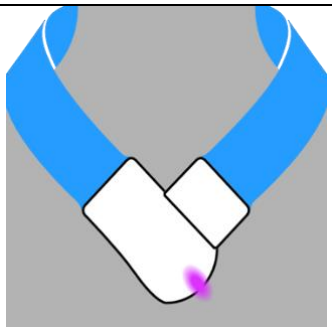
The LED on the Charger will show different things based on how it is being used.

While Unlatched

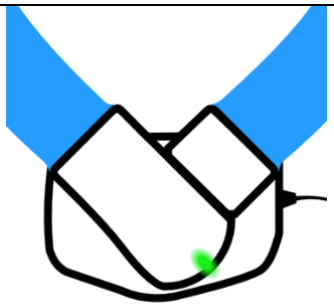
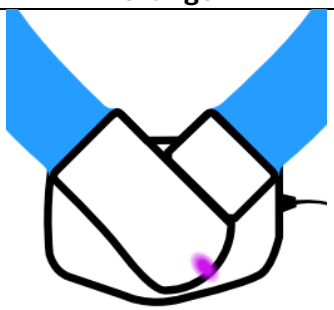
LED Color	Status
 **Green**	**Solid**: The Charger has enough charge to charge the Implant.
 **Orange**	**Solid**: The Charger does not have enough charge to charge the Implant. **Blink**: The Charger needs to be charged before it can be used, or it will turn off.
 **Pink**	**Slow Blink**: This is a warning. The Charger might be too hot. Make sure to keep it in a cool place and away from direct sunlight. **Rapid Blink**: The Charger has an error that cannot be fixed. Stop using it and **contact your doctor or rheumatologist managing the SetPoint System**.

While Being Worn

LED Color	Status
 **Green**	**Solid**: The Implant is fully charged. **Blink**: The Implant has enough charge.
 **Orange**	**Solid**: The Implant is not fully charged and has not started charging yet. **Blink**: The Implant is charging but is not full yet.
 **White**	**Slow Pulse**: The Charger is trying to connect to your Implant. **Rapid Blink**: The Implant is delivering a dose and charging will start once it is complete.

LED Color	Status
 **Pink**	**Solid**: The Implant is suspended or beyond its 10-year service life and will not deliver doses. If beyond its 10-year service life, the battery will no longer charge. **Slow Blink**: This is a warning. • The band of the Charger might be twisted or bent. Make sure to wear it correctly. • The Charger might be too hot. Make sure to keep it in a cool place and away from direct sunlight. • There might be dirt or lint on the Charger's magnetic latch. Look at the **Cleaning** section in the guide for how to clean the latch. **Rapid Blink**: The Charger has an error that cannot be fixed. Stop using it and **contact your doctor or rheumatologist managing the SetPoint System**.

While on the Docking Station

LED Color	Status
 **Green**	**Solid**: The Charger is fully charged. **Blink**: The Charger has enough charge to charge the Implant.
 **Orange**	**Blink**: The Charger is charging, but not full enough to charge the Implant.
 **Pink**	**Slow Blink**: This is a warning. • The Charger may not be closed properly. The Charger cannot charge if it is not latched. • The Charger might be too hot. Make sure to keep it in a cool place and away from direct sunlight. **Rapid Blink**: The Charger has an error that cannot be fixed. Stop using it and **contact your doctor or rheumatologist managing the SetPoint System**.

Appendix B – Charger Speaker Status

Sound Pattern	Status
Two Beeps That Go *Up* in Tone	The Charger is now connected to your Implant.
Two Beeps That Go *Down* in Tone	The Charger has lost its connection with your Implant.
Repeating Beep	The connection between the Charger and your Implant is not strong enough to start charging.
Three Beeps That Go *Up* in Tone	The Implant has started charging.
Four Beeps, Three Beeps That Go *Up* in Tone and a Fourth Beep That is a Repeat of the Last Tone	The Implant has finished charging.

Appendix C – Docking Station LED Status

LED Color	Indicator Status
 **Blue**	**Solid**: The Charger is fully charged. **Blink**: The Charger is charging.
 **Pink**	**Solid**: The Docking Station is ready for use, but the Charger is not charging.
 **Red**	**Blink**: The Docking Station has an error. • Remove the Charger from the Docking Station. • Check that there are no metal objects on or around the Docking Station. • Place the Charger on the Docking Station again. • Check that the Charger is closed. If the error continues, stop using the Docking Station, and **contact your doctor or rheumatologist managing the SetPoint System**.

Appendix D – Troubleshooting

Docking Station

Event	Cause and Resolution
The Docking Station does not show a **pink** LED when plugged in.	The Docking Station is not getting power. Check if the outlet it is plugged into is working (it is turned on, the GFI is not tripped, and the wall switch is on). If the outlet is fine but the problem continues, **contact your doctor or rheumatologist managing the SetPoint System**.
The Docking Station is **blinking red** on its LED.	This is a warning. • Check that the Charger is closed. • Check that there are no metal objects on or around the Docking Station. The Docking Station cannot charge if there are metal objects present. • The Charger and/or Docking Station might be too hot and cannot charge. Make sure to keep them in a cool place and away from direct sunlight. • Take off the Charger for a few seconds, then put it back on the Docking Station cradle. Sometimes, if it wasn't placed or seated correctly, it can stop the Charger and Docking Station from charging. If the error continues, stop using the Docking Station, and **contact your doctor or rheumatologist managing the SetPoint System**.
The Docking Station shows a **pink** LED when the Charger is placed on it.	If this persists and the LED never turns **blue**, the connection between the Charger and your Docking Station cannot be established. This could be caused by electromagnetic interference. Try changing your location, waiting until a later time, or turning off the suspected source of interference if possible. If using portable RF communications equipment, make sure they are no closer than 12 inches (30 cm) to any part of the Charger or Docking Station.

Charger

Event	Cause and Resolution
The Charger is **slowly blinking pink** on its LED.	This is a warning. • The Charger may not be closed properly. The Charger cannot charge if it is not latched. • The Charger might be too hot. Make sure to keep it in a cool place and away from direct sunlight. • The band of the Charger might be twisted or bent. Make sure to wear it correctly. • There might be dirt or lint on the Charger's latch. Look at the **Cleaning** section in the guide for how to clean the latch. If the Charger continues to **slowly blink pink**, **contact your doctor or rheumatologist managing the SetPoint System**.
The Charger is **rapidly blinking pink** on its LED.	The Charger has an error that cannot be fixed. Stop using it and **contact your doctor or rheumatologist managing the SetPoint System**.
The Charger shows a **solid pink** LED.	The Implant is suspended or beyond its 10-year service life and will not deliver doses. If beyond its 10-year service life, the battery will no longer charge. **Contact your doctor or rheumatologist managing the SetPoint System** to restart therapy, if suspended.
The Charger sounds a repeated beeping tone when worn.	The connection between the Charger and your Implant is not strong enough to start charging. The band of the Charger might be twisted or bent. Make sure to wear it correctly. If the Charger continues the repeated beeping pattern, **contact your doctor or rheumatologist managing the SetPoint System**.
The Charger **slowly pulses white** on its LED when worn.	If this persists and the connection beeps never play, the connection between the Charger and your Implant cannot be established. This could be caused by electromagnetic interference. Try changing your location, waiting until a later time, or turning off the suspected source of interference if possible. If using portable RF communications equipment, make sure they are no closer than 12 inches (30 cm) to any part of the Charger.

Appendix E – 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
47 CFR 2.1074: Identification			
	FCC Declaration of Conformity	(b)	The product complies with the applicable FCC requirements
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
Electrical Appliances and Materials Safety Act			
	TÜV SÜD PSE Diamond Mark	N/A	Tested and certified in accordance with applicable Japanese electrical safety and performance standards for Specified Electrical Appliances and Materials
IEC 60417			
	Non-ionizing Electromagnetic Radiation	5140	To indicate elevated, potentially dangerous, levels of non-ionizing radiation
	Class II Equipment	5172	To identify equipment meeting the safety requirements specified for Class II equipment according to IEC 61140
	For Indoor Use Only	5957	To identify electrical equipment designed primarily for indoor use
IEC 60529			
IP21	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.
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°.
International Efficiency Marking Protocol for External Power Supplies			

	International Efficiency Marking Level VI	N/A	Mark indicating EPS meets the level VI requirements at both 115 V/60 Hz and 230 V/50 Hz
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
	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			
	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: 5.7. 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
UL Solutions Marks and Label Hub			

	UL Recognized Component Mark for US and Canada	N/A	Tested and certified in accordance with applicable US and Canadian electrical safety and performance standards
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

47 CFR 2 Frequency Allocations and Radio Treaty Matters: General Rules and Regulations – Equipment Authorization Procedures

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)

Electrical Appliances and Materials Safety Act Statutory Operations and Implementation Guide (ver. 4.0)

IEC 60417:2024 Graphical Symbols for use on Equipment

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

International Efficiency Marking Protocol for External Power Supplies Version 3.0, September 2013

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 F – SetPoint System Technical Description

Implant

Power Source

The Implant is internally powered by a rechargeable battery.

Characteristic	Value
Type	Secondary (Rechargeable)
Chemistry	Lithium-ion (Li-ion)
Form Factor	Cylindrical
Voltage	4.0 V (Nominal)
Capacity	3.0 mAh
Safety Features	Zero-Volt Technology

Table 3 – Implant Battery Characteristics

The rechargeable battery is rated to last for 10 years, and this duration is not impacted by any Implant settings, (e.g., the strength or timing of stimulation).

Charger

⚠ **Warning:** Do not modify or tamper with the SetPoint Charger. If you do, it could alter its function or bypass safety features and result in harm.

Classification

Per IEC 60601-1, the Charger does not meet the definition of an Applied Part, only of an Accessible Part. Per clause 4.6, and per risk assessment, it was, however, tested to the more rigorous Applied Part requirements. The table below shows the relevant technical classifications for the Charger per IEC 60601-1 and collateral standards.

Classification	Value
Accessibility	Type BF, Applied Part
Power Source	Internally Powered
Mode of Operation	Continuous
Operating Environment	Home Healthcare
Transportability	Body-Worn
Transit Operability	Transit-Operable
Ingress Protection	IP22

Table 4 – Charger As-Tested Classifications

Per IEC 60601-1, the user is classified as a Patient only while the Charger is latched around their neck, and as an intended Operator while placing or removing the Charger around their neck or onto or from the Docking Station.

Power Source

The Charger is internally powered by a non-replaceable, rechargeable battery.

Characteristic	Value
Type	Secondary (Rechargeable)

Chemistry	Lithium-ion (Li-ion)
Form Factor	Pouch
Voltage	3.7 V (Nominal)
Capacity	1.0 Ah
Safety Features	Over Charge, Over Discharge, and Over Current Detection

Table 5 – Charger Battery Characteristics

On a full charge, the rechargeable battery can power the Charger for 20 to 60 minutes depending on the placement of the Charger around the neck and how optimally it is communicating with the Implant. The rechargeable battery is rated to last for 5 years, and this duration is not impacted by how the Charger is used.

Radios

The Charger contains a Bluetooth Low Energy (BLE) radio receiver that receives RF electromagnetic energy in the frequency range 2.400 GHz to 2.4835 GHz. The Charger also contains an additional inductive radio that transmits electromagnetic energy. The radio specifications are as follows:

Characteristic	Value	
	BLE Radio	**Inductive Radio**
Frequency Range	2.400 GHz – 2.4835 GHz	127.6 kHz – 134.4 kHz
Modulation Type	GFSK, 1Mbps	AM 2400 bps
EIRP	2.5 mW (+4 dBm)	Not Defined, Total Power ≤ 6 W

Table 6 - Radio Transmit Details

Product Markings

All Charger product markings are contained on the Charger label shown below (artwork shown is for reference only).

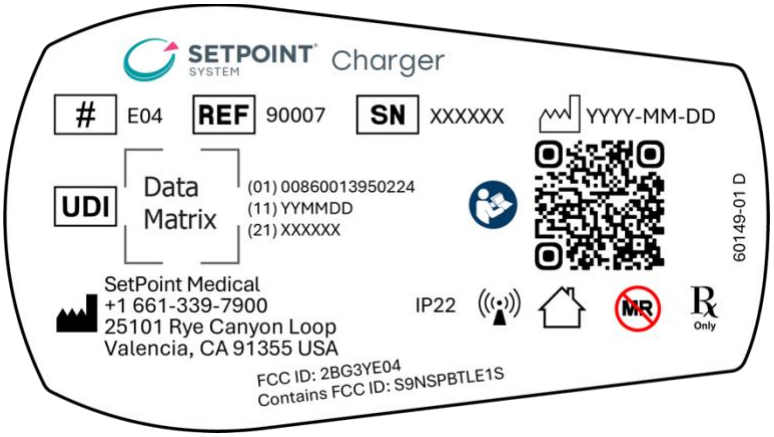


Figure 17 – Charger Label

Docking Station

⚠ **Warning:** Do not modify or tamper with the SetPoint Docking Station. If you do, it could alter its function or bypass safety features and result in harm.

Classification

The table below shows the relevant technical classifications for the Docking Station per IEC 60601-1 and collateral standards.

Classification	Value
Accessibility	Accessible Part
Power Source	Externally Powered Class II
Mode of Operation	Continuous
Operating Environment	Home Healthcare
Transportability	Portable
Transit Operability	Non-Transit-Operable
Ingress Protection	IP21

Table 7 – Docking Station Classifications

Per IEC 60601-1, the user is classified as an intended Operator while placing or removing the Charger onto or from the Docking Station.

Power Source

The Docking Station is externally powered through a power supply cord to a power supply with a mains-plug that can be removed from the mains socket-outlet to provide supply mains isolation. This non-detachable power supply cord is not replaceable.

Characteristic	Value
Input Type	AC
Input Voltage	100-240 VAC
Input Frequency	50-60 Hz
Input Max Current	1.0-0.5 A
Output Type	DC
Output Voltage	5 V
Output Max Current	2.4 A

Table 8 – Docking Station Power Supply Performance Characteristics

Product Markings

All Docking Station product markings are contained on the Docking Station and power supply labels shown below (artwork shown is for reference only).

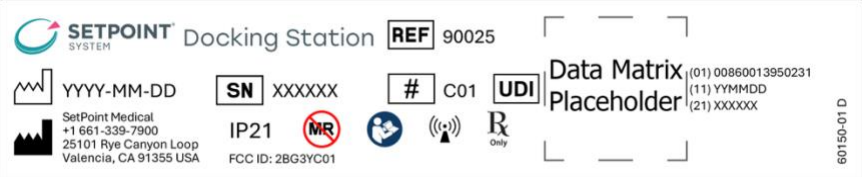


Figure 18 – Docking Station Label

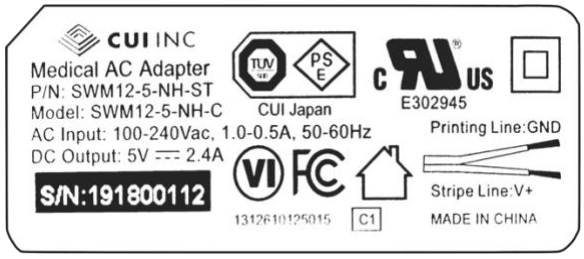


Figure 19 – Docking Station Power Supply Label

Charger and Docking Station

Emissions and Immunity Testing

The Charger and Docking Station are classified as CISPR 11 Class B Group 2 emitters. Both devices were tested with immunity test levels for use in a home healthcare environment. They were found to comply with the following immunity test standards at the specified test levels:

IEC 61000-4-2 – Charger and Docking Station Electrostatic Discharge

Device	Contact Discharge (± kV)	Air Discharge (± kV)
Charger	8	2, 4, 8, 15
Docking Station	N/A	

Table 9 - IEC 61000-4-2 Test Details

IEC 61000-4-3 – Charger and Docking Station Radiated RF EM Fields and Proximity Fields from RF Wireless Communications Equipment

- Radiated RF EM Field Exposures: 10 V/m from 80 MHz – 2.7 GHz w/80% Amplitude Modulation @1 kHz
- Proximity Field Exposures:

Test Frequency (MHz)	Modulation	Immunity Test Level (V/m)
385	Pulse, 18 Hz	27
450	Pulse, 18 Hz	28
710, 745, 780	Pulse, 217 Hz	9
810, 870, 930	Pulse, 18 Hz	28
1720, 1845, 1970, 2450	Pulse, 217 Hz	28
5240, 5500, 5785	Pulse, 217 Hz	9

Table 10 - IEC 61000-4-3 Test Details (Pulse = 50% Square Wave Duty Cycle

IEC 61000-4-4 – Docking Station EFT/Burst

- ± 2 kV @100 kHz Repetition Frequency

IEC 61000-4-5 – Docking Station Line to Line Surge

- ± 0.5 kV and ± 1 kV

IEC 61000-4-6 – Docking Station Conducted Disturbances

- 3 V_{rms} from 150 kHz – 80 MHz
- 6 V_{rms} from 150 kHz – 80MHz for ISM and Amateur Radio Bands w/80% Amplitude Modulation @1 kHz

IEC 61000-4-8 – Charger and Docking Station Rated Power Frequency Magnetic Field

- 30 A/m @60Hz

IEC 61000-4-11 – Docking Station Voltage Dip and Interruption

- 100 VAC and 240 VAC @60 Hz

Voltage Level	Duration (cycles)	Phase Angle
0% of U_t	0.5	0°, 45°, 90°, 135°, 180°, 225°, 270°, 315°
0% of U_t	1	0°
70% of U_t	30	0°
0% of 120 V	300	0°

Table 11 - IEC 61000-4-11 Test Details (U_t = 100 V or 240V)

IEC 61000-4-39 – Charger and Docking Station Proximity Magnetic Field

Test Frequency	Modulation	Immunity Test Level (A/m)
30 kHz	CW	8
134.2 kHz	Pulse, 2.1 kHz	65
13.56 MHz	Pulse, 50 kHz	7.5

Table 12 - IEC 61000-4-39 Test Details (Pulse = 50% Square Wave Duty Cycle)

FCC Compliance

This device complies with part 15 of the FCC Rules. Operation is subject to the following two conditions: (1) this device may not cause harmful interference, and (2) this device must accept any interference received, including interference that may cause undesired operation.

Note: This equipment has been tested and found to comply with the limits for a Class B digital device, pursuant to part 15 of the FCC Rules. These limits are designed to provide reasonable protection against harmful interference in a residential installation.

This equipment generates, uses, and can radiate radio frequency energy and, if not installed and used in accordance with the instructions, may cause harmful interference to radio communications. However, there is no guarantee that interference will not occur in a particular installation.

If this equipment does cause harmful interference to radio or television reception, which can be determined by turning the equipment off and on, the user is encouraged to try to correct the interference by one or more of the following measures:

- Reorient or relocate the receiving antenna.
- Increase the separation between the equipment and receiver.
- Connect the equipment to an outlet on a circuit different from that to which the receiver is connected.
- Consult the dealer or an experienced radio/TV technician for help.

Changes or modifications not expressly approved by SetPoint Medical could void your authority to operate the equipment.

To maintain compliance with the FCC's RF exposure guidelines, the Docking Station should be installed and operated with a minimum distance of 8 in (20 cm) between it and your body.

Appendix G – 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**).

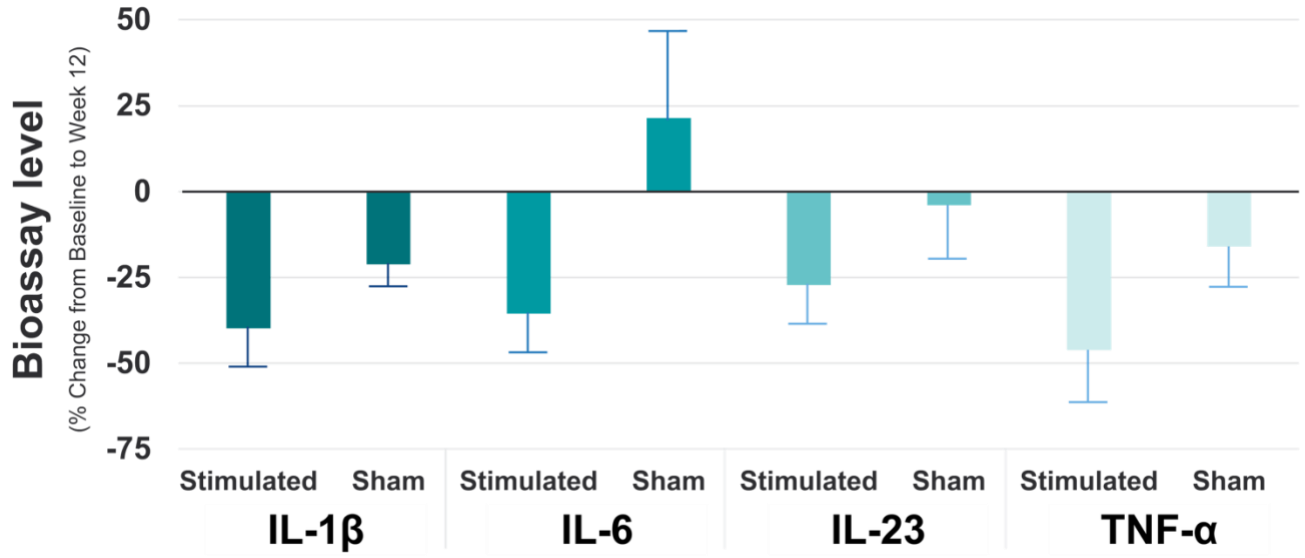


Figure 20 - Percent change from the Day 0 visit in proinflammatory cytokines levels in the TruCulture ex vivo bioassay (mean ± SME)

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**).

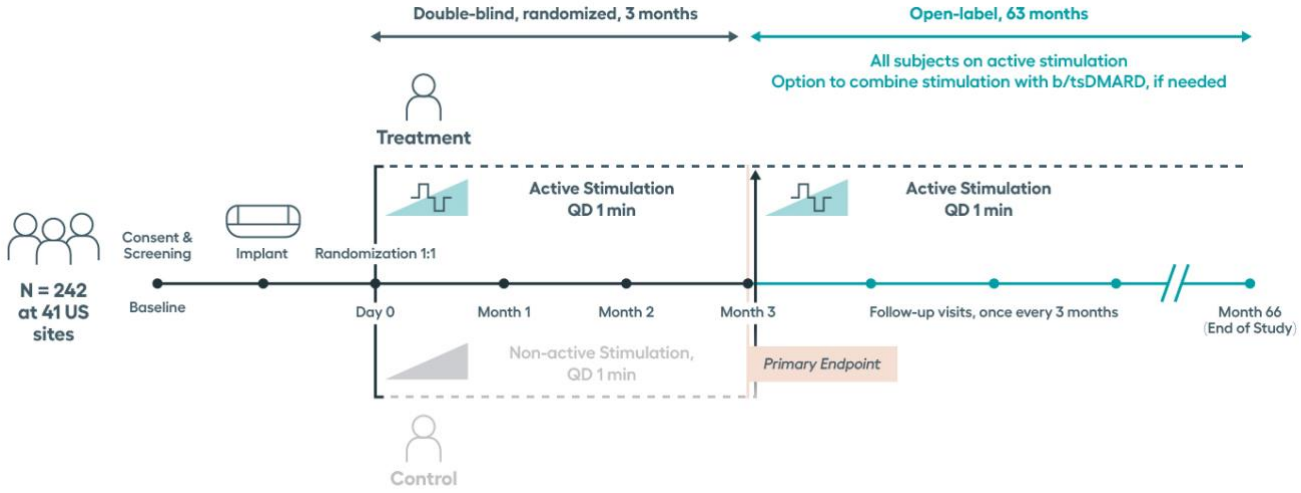


Figure 21 - RESET-RA Study Schematic

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 13**.

	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 13 - Baseline Demographics of Patients in RESET-RA Study

Medical history of prior biological and targeted synthetic DMARDs (b/tsDMARDs) is presented in **Table 14**.

	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 14 - Baseline Prior b/tsDMARD History

Table 15 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 15 - 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 16**.

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 16 – Related, Serious AEs from Implantation Procedure to Week 12

Non-serious AEs related to the implantation procedure and/or Implant are summarized in **Table 17**. 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 17 - 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 18**).

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 18 - 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 19**). 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 19 - 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 20**).

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 20 - 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 21.** 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 21 - 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 22**).

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

Table 23 and **Table 24** 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 23 - 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 24 - 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 25** and **Table 26**, 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 25 - 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 26 - 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 27**.

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 27 - 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 28**.

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 28 - 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 29**.

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 29 - 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 30**).

	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 30 - Patient Satisfaction and Recommendation at Week 24

Appendix H – Cybersecurity

IT Configuration

A guide for more advanced IT configuration of the SetPoint System can be found on the SetPoint Medical Website at https://spm.care/manuals. The IT guide contains the following information:

- Detailed technical descriptions of minimum networking requirements
- Diagrams for the home and healthcare use environment
- A list of all addresses and ports the SetPoint System uses for its connectivity
- Recommended networking encryption protocols
- Recommendations for IT-related cybersecurity hardening
- Details on data integrity and backup procedures
- Troubleshooting related to IT issues

Cybersecurity Software Updates

Known cybersecurity vulnerabilities found in the SetPoint System will be published as advisories on the SetPoint Medical website. Any advisories can be found at https://spm.care/cybersecurity-advisories. Software and firmware updates that remediate cybersecurity vulnerabilities can be obtained by bringing your SetPoint Medical devices to your healthcare professional.

Data Integrity, Backup, and Recovery

A fundamental tenet of the SetPoint System's data strategy is about what data is *not* collected or stored. Every effort is made to avoid collecting, transmitting, or storing data unless it is necessary to the functionality of the system. For example, none of the following pieces of information are ever stored on the Implant or Charger:

- Patient Names
- Usernames or Emails
- Location or Address Information
- Clinic Information
- Phone Numbers
- Date of Birth
- Race or Gender Information

Implant Integrity and Backups

The Implant ensures the integrity on all its non-volatile memory. In certain critical spaces, such as therapy parameters, redundant copies of data are kept. Where redundant data is available, and corruption or tampering is detected, an attempt will be made to restore a known-valid copy of the data. If corruption is detected on non-volatile program memory, the device will return to its bootloader – a state which is displayed on the Charger so that the user is made aware (see **Appendix A - Charger LED Status**).

Integrity checks are performed routinely, including every time an Implant is charged and every time an Implant powers up to perform autonomous stimulation. Therapy parameters are kept safe with redundant copies on the Implant. They are also preserved in the Cloud. Should all therapy parameters on the Implant be corrupted or erased, they will be automatically restored by Programmer fetching the data from the Cloud during the next clinic visit.

Charger Integrity and Backups

The Charger also ensures the integrity of all its non-volatile memory. In certain critical spaces, redundant copies of data are kept. Where redundant data is available, and corruption or tampering is detected, an attempt will be made to restore a known-valid copy of the data. If corruption is detected on non-volatile program memory, the device will return to its bootloader – a state which is displayed on the Charger so that the user is made aware (see **Appendix A - Charger LED Status**). Integrity checks are performed routinely, including every time the Charger is placed on the Docking Station.

Decommissioning and Sanitizing the Charger's Data

The Charger stores the following Implant information in its non-volatile memory:

- A cached Implant Event Log, including the last-connected Implant's Model ID and Serial Number
- Key information for encryption with the Implant

This data is erased when connected to a new Implant. Only authorized and authenticated healthcare professionals are allowed to issue commands to read this data. The Charger leverages chip Readout Protection (RDP) modes to prevent any debuggers from accessing this data. Attempts to access this data with a debugger will result in erasing all memory on the device. No explicit steps are needed to sanitize or decommission a Charger.

Decommissioning and Sanitizing the Implant's Data

The Implant does not support deleting its data. **Contact SetPoint Medical to request a return merchandise authorization (RMA)** for the explanted Implant, if removed.

Responding to Cybersecurity Events

If you suspect a cybersecurity event has occurred, **contact SetPoint Medical**. SetPoint Medical has a team that monitors for cybersecurity events and will promptly respond to any cybersecurity threats. If you believe you have discovered a cybersecurity vulnerability in a SetPoint Medical product, please follow SetPoint Medical's Coordinated Vulnerability Disclosure process which can be found at https://spm.care/security.

Software Bill of Materials

An up-to-date Software Bill of Materials (SBOM) can be found on the SetPoint Medical Website at https://spm.care/sbom.

Cybersecurity End-of-Support

Cybersecurity support is offered through the expected operating duration of the devices (i.e., 5 years for the Charger and 10 years for the Implant). During this time, patients and healthcare professionals can expect cybersecurity updates to the Implant and Charger to address any vulnerabilities that may be discovered.