SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Vagus nerve stimulator for rheumatoid arthritis

Device Trade Name: SetPoint System

Device Product Code: SFJ

Applicant's Name and Address: SetPoint Medical
25101 Rye Canyon Loop
Valencia, CA 91355 U.S.A.

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P240039

Date(s) of the FDA Notice of Approval: July 30, 2025

Breakthrough Device:
Granted breakthrough device status on March 15, 2024, because the device (1) could provide for more effective treatment of moderate to severe rheumatoid arthritis, a life-threatening or irreversibly debilitating human disease, and (2A) represents breakthrough technology that (2C) offers significant advantages over existing approved or cleared alternatives, and (2D) device availability is in the best interest of patients.

II. INDICATIONS 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).

III. CONTRAINDICATIONS

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

The SetPoint System should not be used:

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

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the SetPoint System labeling.

V. DEVICE DESCRIPTION

The SetPoint System includes:

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

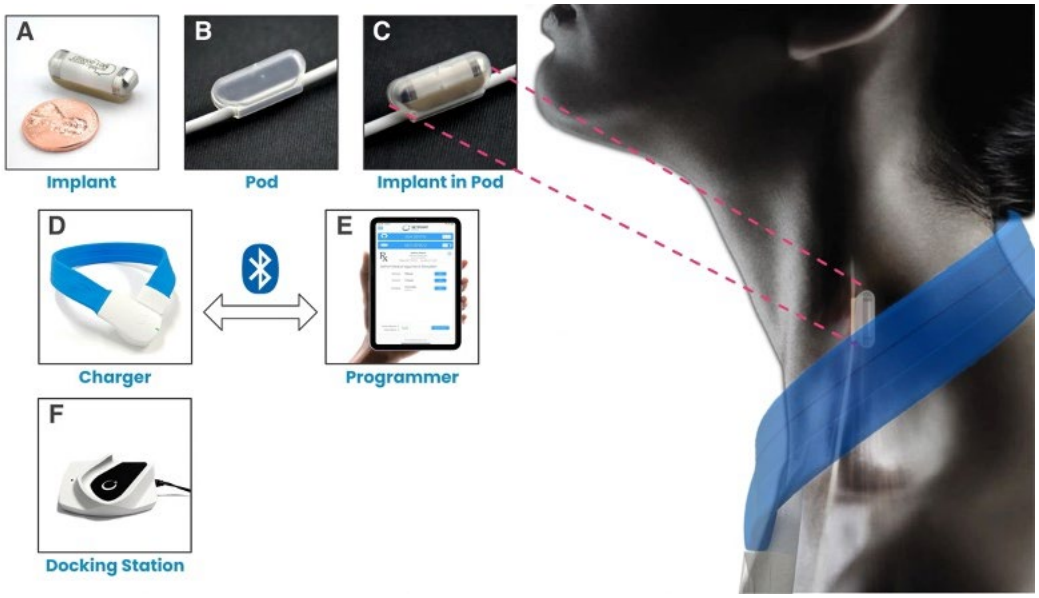

Figure 1: SetPoint System and Components

Implant and Pod

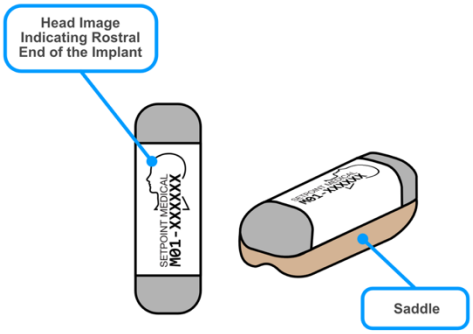

Figure 2: Implant

The Implant is an integrated neurostimulation device. It is used to electrically stimulate the vagus nerve for 1 minute, once daily. It is about 1 in (2.5 cm) long and weighs about 0.1 oz (3 g). A surgeon implants it 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

holds the Implant in place, such that the nerve is held in the Pod's groove, and the Pod is closed with a suture using the suture holes on either side of the Pod Opening.

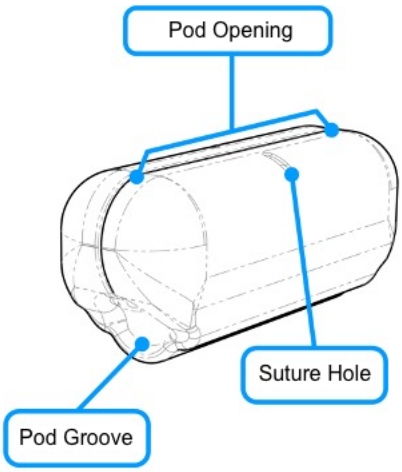

Figure 3: Pod

Charger

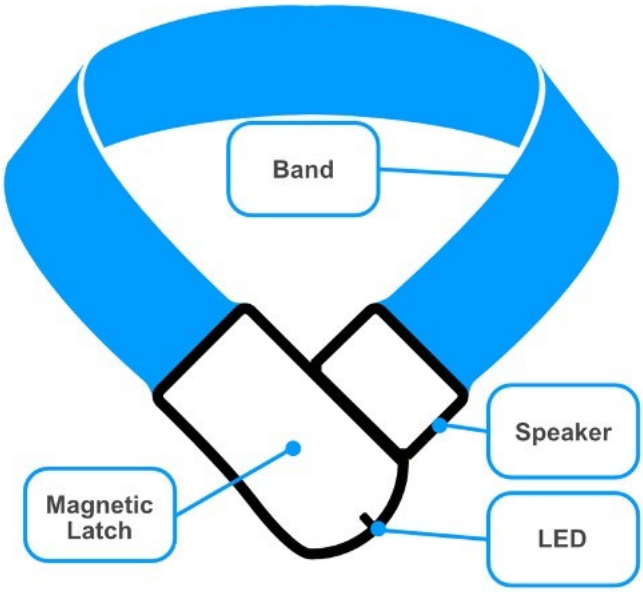

Figure 4: Charger

The Charger is a device worn around the patient's neck. It is used for charging the Implant at home and for programming the Implant at the clinic. It is recommended to be worn once a week for about 10 minutes 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 a light-emitting diode (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, it

is necessary to perform a fit and tolerability test on the patient to make sure it fits comfortably around their neck and that the magnetic latch closes.

Docking Station

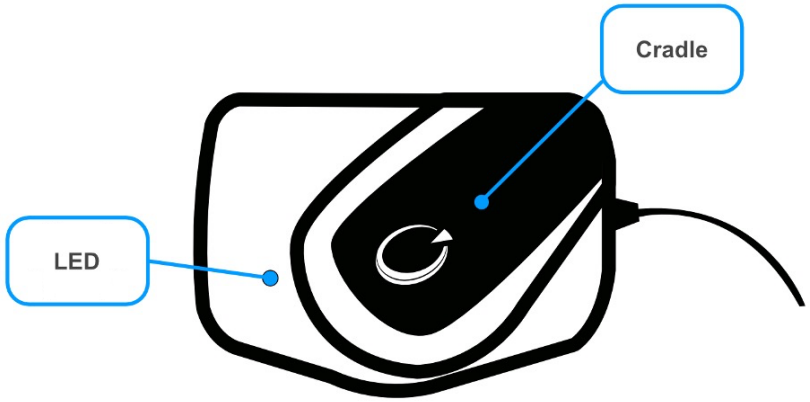

Figure 5: The Docking Station

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.

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 in which the Charger is placed, and a power cord that must be plugged into an electrical outlet.

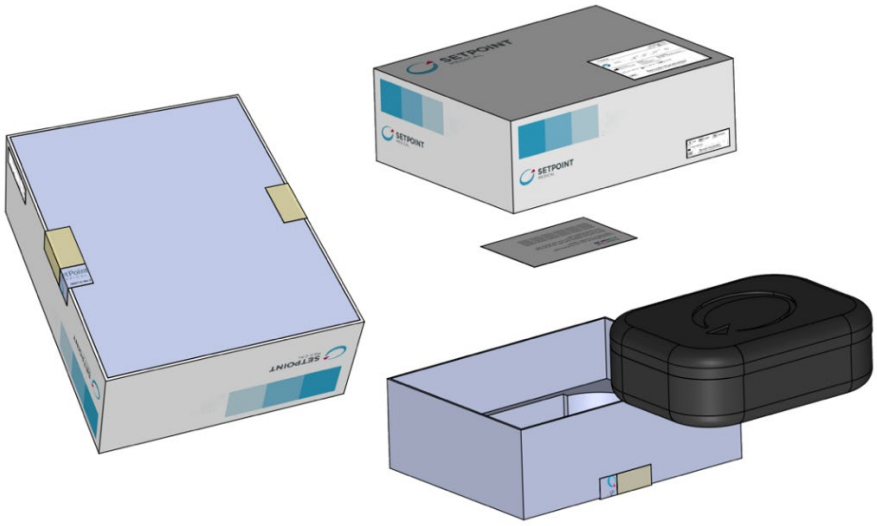

Figure 6: Carrying Case Inside Sealed Product Box

Programmer

The Programmer is an app installed on an Apple iPad® that is only used by an authorized healthcare professional. It is used with the Charger to program the Implant or to turn off or resume stimulation, if necessary. Additionally, it gives healthcare professionals

information about the use of the Implant and Charger, such as how many stimulation doses have been delivered or missed, and Implant battery charge levels.

Strength, Mode of Administration

The SetPoint System automatically delivers stimulation once per day, for a duration of 1 minute. Strength of stimulation is titrated to the maximum strength tolerated, with a maximum allowed amplitude of 2500μA and pulse width of 250 μs equivalent to 6.05 $\mu C/cm^2$ charge density) at 10 Hz.

Patient Identification (ID) Card

The Patient ID Card is included in the Implant packaging. The Patient ID Card is filled out and provided to the patient after the surgery, and before they leave the hospital. Additionally, the QR code on the card provides access to critical information regarding the Implant, which is necessary to ensure that any diagnostic procedures and other medical treatments are compatible with the SetPoint System. The Patient ID Card identifies the Implant and Pod as magnetic resonance (MR) conditional, which means the Implant and Pod were demonstrated to be safe in the MR environment within defined conditions, including conditions for the static magnetic field, the time-varying gradient magnetic fields, and the radiofrequency fields.

Patients are instructed by their surgeon to always have their Patient ID card on hand to present to healthcare professionals (such as physicians, dentists, imaging technicians (e.g., MRI, X-ray), estheticians, or beauty-care specialists), before pursuing any additional medical imaging or treatments, and during security screenings, such as at airports. Neglecting to inform these professionals about the Implant may result in injury to the patient, cause harm to the SetPoint System, and/or may lead to complications with the procedure or treatment. If the patient changes doctors, or loses their card, they should contact SetPoint Medical for a replacement card.

Therapy Parameters Card

The SetPoint System provides stimulation to the patient for one minute each day, occurring at the same time each day. Although patients may be safely scanned using MRI anywhere in the body two weeks after implantation, MRI scans must never overlap with the time of stimulation of the implant, even after this two-week post-implantation window. To avoid this, patients are provided with a Therapy Parameters Card that documents the time of stimulation for their device and instructed to always present this card to healthcare professionals prior to scheduling an MR procedure. The card instructs healthcare providers to schedule MRI imaging such that the MRI will not occur within ±1 hour from the time documented on the patient's Therapy Parameters Card. However, if the implant is suspended or expired, this restriction is unnecessary.

VI. ALTERNATIVE PRACTICE AND PROCEDURES

Currently, there are no FDA approved devices marketed for the treatment of RA. There are multiple approved pharmaceutical alternatives for the treatment of RA. Standard of care treatment options (SOC) for patients with moderate to severe RA include several FDA approved disease-modifying anti-rheumatic drugs (DMARDs) such as conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs), and target synthetic DMARDs (tsDMARDs), which include Janus Kinase inhibitors (JAKi) (see **Table 1**).[1] Each alternative has its own advantages and disadvantages. A patient

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

Table 1: Disease-Modifying Anti-Rheumatic Drugs (DMARDs) for Rheumatoid Arthritis

Category	Use of DMARD	Examples
conventional-synthetic DMARD (csDMARD)	Typically, the initial DMARD prescribed. Only DMARD that may be used in combination with another DMARD. Typically taken orally or subcutaneously.	methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine
biological DMARD (bDMARD)	Used after an inadequate response or intolerance to a csDMARD. Administered by subcutaneous injection (Sub-Q) or intravenous infusion (IV).	TNF inhibitors (e.g., etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T-cell costimulatory inhibitor (abatacept), IL-6 receptor inhibitors (tocilizumab, sarilumab), anti-CD20 antibody (rituximab) and approved bio similar bDMARDs
targeted-synthetic DMARD (tsDMARD)	Used after inadequate or intolerant response to one or more bDMARDs (referred to as bDMARD-IR). Most recently approved drug class for RA. Taken by oral administration.	tofacitinib, baricitinib, upadacitinib (collectively referred to as JAK inhibitors)

VII. MARKETING HISTORY

The SetPoint System has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications, side effects) associated with the use of the device:

Implantation and Explantation Surgery

Potential risks with surgical placement or removal of the Implant and Pod, as well as other devices that stimulate the left vagus nerve, include:

- Complications related to general anesthesia with intubation.
- Damage such as stretching, pinching or cutting of the vagus nerve. The most common symptoms are caused by an injury to a branch of the vagus nerve that innervates a muscle in the throat, resulting in hoarseness or other voice change, or a change in breathing or swallowing. If the vagus nerve is damaged during surgery, unilateral vocal cord dysfunction (paresis) or paralysis may occur. Swallowing difficulties can lead to aspiration and pneumonia. Recovery of vocal cord function may require voice therapy and/or vocal cord augmentation filler injections in order to accelerate return to normal functioning. While these symptoms typically resolve over time (weeks to months), in rare cases, they can be permanent.
- Damage due to compression of the cervical sympathetic chain that goes to the left eye can result in Horner's Syndrome, a contracted (smaller) pupil (miosis), a droopy upper eyelid (ptosis), and/or inability to sweat on the left side of the face (anhidrosis).
- Damage to other muscles, nerves, blood vessels or tissues around the surgical area.
- Excessive bleeding or stroke due to blood vessel injury or blockage.
- Postoperative pain, redness, soreness, inflammation, fluid build-up under the skin,

itching or swelling at the implant site.
- Scarring or infection of tissue around the area of device placement or removal. Infections can usually be treated with antibiotics but may require that the device be surgically removed.
- Belching (eructation), constipation, vomiting or gagging.
- Removal of the Implant and Pod is associated with a higher occurrence of the risks above because of possible scarring around the Implant. There is also the possibility that surgical removal is attempted, but during the procedure, the surgeon decides the Implant and Pod cannot safely be removed.

Stimulation

Common side effects reported for the SetPoint System and other similar devices that stimulate the vagus nerve to treat different diseases are:

- Coughing
- Neck or facial pain
- Hoarseness or other voice disturbances (dysphonia)
- Shortness of breath (dyspnea)
- Throat pain, a burning sensation, or inflammation of the back of the throat (pharyngitis)
- Swallowing difficulties (dysphagia) that could lead to aspiration.
- Tingling, prickling or numbness sensations near the implant site (paresthesias)
- Nausea and indigestion
- Constipation
- Belching (eructation)
- Flu-like symptoms
- Dizziness

These symptoms may occur during the time the Implant is delivering electrical stimulation. However, these symptoms may not occur in people who are less sensitive to stimulation than others.

Uncommon Side Effects Include:

- Worsening of pre-existing pulmonary diseases, such as asthma and chronic obstructive pulmonary disease
- The Implant may move slightly from its original location, and this might cause damage to the vagus nerve, other nerves, blood vessels, or other surrounding tissue in the body
- The Implant, or any of its parts, can break, in which case the stimulation may not be delivered correctly
- Worsening or new onset of sleep apnea
- Change in heart rate or rhythm (the heart may beat too fast, too slowly, too early, or irregularly)
- Headaches
- Flushing
- Vomiting
- Gagging

- Weight change (loss or gain)
- A decrease in blood pressure that could result in fainting (syncope)
- Sleep disturbance
- Dental pain
- Dysgeusia

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Implantable Components (Implant and Pod)

Key testing on the Implantable Components of the SetPoint System, the Implant and Pod, is summarized in **Table 2**, including the test, purpose, acceptance criteria, and results for each test.

Table 2: Implantable Components Testing Summary

Test	Purpose	Acceptance Criteria	Results
Software / Firmware Verification and Validation Testing	To verify that software and firmware meet user needs and perform as intended, in accordance with the FDA guidance, "Content of Premarket Submissions for Device Software Functions," issued on June 14, 2023, and demonstrate compliance to the ANSI/AAMI/IEC 62304:2006 Medical device software - Software life-cycle processes industry standard.	The software system shall meet the SetPoint System requirements and function as intended.	PASS
Cybersecurity Testing	To verify that the SetPoint System complies with cybersecurity controls in accordance with FDA's cybersecurity guidance, "Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions."	The software system prevents unauthorized access, modification, misuse or denial of use of a medical device, or the unauthorized use of information that is stored, accessed, or transferred from a medical device to an external recipient.	PASS
Engineering/ Bench Testing	To verify accuracy of device output specifications for stimulation parameters, battery life and communication with the external components.	The Implantable Components meet all the identified operational requirements.	PASS
Mechanical Testing	To verify that the SetPoint System meets appropriate standards for mechanical shock, vibration and environmental conditions of temperature and pressure.	The SetPoint System shall meet the mechanical safety requirements identified in ISO 14708-1.	PASS

Electrical Safety and EMC Testing	To verify that the SetPoint System meets appropriate standards for electrical safety.	The SetPoint System shall meet the electrical safety and EMC requirements identified in ISO 14708-3.	PASS
Thermal Testing	To verify the thermal safety of the Implantable Components of the System.	The SetPoint System shall meet the thermal safety requirements identified in ISO 14708-3.	PASS
Sterilization Testing	To demonstrate that the process complies with ISO 11135:2014/ AMD 1: 2018 and meets acceptance criteria.	The sterilization process shall provide a minimum sterility assurance level (SAL) of 10^{-6}.	PASS
Packaging and Shelf-Life Verification Testing	To verify the integrity of the primary and secondary packaging per ISO 11607-1:2019 as directed by ISO 14708-1. To validate the labeled shelf-life of 12 months.	The packaging of the Implantable Components shall meet the requirements of ISO 11607-1 and ISO 14708-1.	PASS
Ultrasound Compatibility Testing	To verify the implantable components can withstand exposures typical during a diagnostic ultrasound examination.	The implantable components pass visual and functional testing after exposure to diagnostic levels of ultrasound energy.	PASS
MRI Compatibility Testing	To verify the MRI compatibility of the implantable components in the MRI environment.	The implantable components (Implant and Pod) are considered MRI conditional (1.5 T- 3.0 T) for its intended use.	PASS

External Components (Charger and Docking Station)

Key testing on the External Components of the SetPoint System, the Charger and Docking Station, is summarized in **Table 3**, including the test, purpose, acceptance criteria, and results for each test.

Table 3: External Components Testing Summary

Test	Purpose	Acceptance Criteria	Results
Software / Firmware Verification and Validation Testing	To verify that software and firmware meets user needs and performs as intended, in accordance with the FDA guidance titled "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" and demonstrate compliance to the ANSI/AAMI/IEC 62304:2006 Medical device software - Software life cycle processes industry standard.	The software system shall meet the SetPoint System requirements and function as intended.	PASS
Cybersecurity Testing	To verify that the SetPoint System complies with cybersecurity controls in accordance with FDA's cybersecurity guidance, "Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions."	The software system prevents unauthorized access, modification, misuse or denial of use of a medical device, or	PASS

Test	Purpose	Acceptance Criteria	Results
		the unauthorized use of information that is stored, accessed, or transferred from a medical device to an external recipient.	
Engineering/ Bench Testing	To verify accuracy of device operations, battery life, and communication with the implantable components.	The external components meet all the identified operational requirements.	PASS
Mechanical Testing	To verify that the SetPoint System meets appropriate standards for mechanical shock, vibration and environmental conditions of temperature and pressure.	The external components of the SetPoint System shall meet the mechanical safety requirements identified for basic safety and use in the home healthcare environment in IEC 60601-1 and IEC 60601-1-11.	PASS
Electrical Safety and EMC Testing	To verify that the SetPoint System meets appropriate standards for electrical safety.	The SetPoint System shall meet the electrical safety and EMC requirements identified in IEC 60601-1.	PASS
Thermal Testing	To verify the thermal safety of the external components of the SetPoint System.	The SetPoint System shall meet the thermal safety requirements identified for basic safety in IEC 60601-1.	PASS
Packaging Testing	To verify the integrity of the primary and secondary packaging when exposed to shipping exposures.	The packaging of the external components shall meet the requirements of ASTM D4169-22 and associated standards for performance testing of shipping containers.	PASS
Federal Communication Commission (FCC) Testing	To verify the safety of Radiofrequency (RF) electromagnetic radiation exposure driven by 47 CFR 2.1093.	The Specific Absorption Rate (SAR) values do not exceed the limits for local or whole body SAR per FCC regulations.	PASS

B. Biocompatibility

Biocompatibility testing was performed for the patient-contacting components of the SetPoint System (i.e., the implant and pod) in accordance with ISO 10993-1 and the FDA Guidance Document, "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" and in compliance with Good Laboratory Practices (GLP), 21 CFR Part 58. The biocompatibility endpoints listed in **Table 4** were assessed. The results of testing demonstrate that the components of the SetPoint System are biocompatible for its intended use.

Table 4: Summary of Biocompatibility Testing

Biological Effect (Applicable Standard)	Test Method	Results
Long-Term, Intact Skin Contacting Component: Charger		
Cytotoxicity (ISO 10993-5)	MEM Elution	Non-cytotoxic
Irritation, Intracutaneous Reactivity (ISO 10993-23)	Intracutaneous Reactivity Test	Non-irritant
Sensitization, Maximization Sensitization (ISO 10993-10)	Guinea Pig Maximization Sensitization Test	Non-sensitizing
Permanent, Long-Term (>30 days) Components in Contact with Neural Tissue/Bone: Implant and Pod		
Cytotoxicity (ISO 10993-5)	MEM Elution	Non-cytotoxic
Irritation, Intracutaneous Reactivity (ISO 10993-23)	Intracutaneous Reactivity Test	Non-irritant
Sensitization, Maximization Sensitization (ISO 10993-10)	Guinea Pig Maximization Sensitization Test	Non-sensitizing
Systemic Toxicity (Acute (ISO 10993-11)	Acute Systemic Injection	No acute systemic toxicity
Systemic Toxicity (Subacute, Subchronic, Chronic (ISO 10993-11)	Chronic Animal Study	Acceptable systemic toxicity risks
	Analytical Chemical Characterization and Toxicological Risk Assessment	
Materials Mediated Rabbit Pyrogenicity (ISO 10993-11)	Materials-Mediated Rabbit Pyrogen Test	Non-pyrogenic
Genotoxicity (ISO 10993-3 and ISO 10993-33)	Bacterial Reverse Mutagenicity Test	Non-genotoxic
	In Vitro Mouse Lymphoma Assay with Extended Treatment	

Biological Effect (Applicable Standard)	Test Method	Results
Local Effects after Implantation (ISO 10993-6)	Twelve canines with equal number of each sex were implanted with the device on the left vagus nerve, with sham procedures completed on the right vagus nerve. After 14 days of healing, the Implant was stimulated with the animals survived as follows: · Cohort 1 (N=6): Day 15-Day 42 · Cohort 2 (N=6): Day 15-Day 180 Pathological assessment and the changes noted on histological examination did not generate concerns for tissue safety; findings were attributed to the presence of a device around the implanted nerve for the in-life duration and were considered to be non-significant compared to sham control. Devices were then put in standby mode, perform device explants and necropsies.	Acceptable implantation risks
Carcinogenicity (ISO 10993-3)	Analytical Chemical Characterization and Toxicological Risk Assessment	Non-carcinogenic

C. Human Factors and Usability

Surgeon, Prescriber, and Patient usability studies were conducted per IEC 62366-1, Medical devices – Part 1: Application of usability engineering to medical devices, FDA guidance document, "Applying Human Factors and Usability Engineering to Medical Devices," issued on February 3, 2016.

Usability testing was conducted to evaluate whether three user groups - Surgeons (N=15), Prescribers (N=16), and Patients (N=16) - can safely and effectively perform all critical tasks associated with their respective use of the SetPoint System. Additionally, the studies were conducted to confirm that use-related risks associated with Surgeon, Prescriber, and Patient use of the SetPoint System were appropriately captured and assessed in the Use-Related Risk Analysis, and to uncover any unforeseen use errors. The testing was designed to test the unique aspects of the device for usability, not standard practice tasks and standard-of-care medical care tasks performed in the same manner regardless of the surgical procedure or specific VNS manufacturer.

Usability testing was completed successfully in simulated intended use environments for the Surgeon, Prescriber, and Patient user groups. Based on both objective and subjective input across the Surgeon, Prescriber, and Patient usability validation studies, use-related risks have been eliminated or have residual risk that is considered acceptable. Use-related risks associated with use of the SetPoint System were appropriately captured in the Use-Related Risk Analysis and no previously unforeseen use errors were uncovered in the study.

As the final device design was evaluated in usability testing but not in subjects enrolled in the pivotal study, SetPoint Medical is required per Conditions of Approval to provide real-world

data via a Post-Approval Study ("SetPoint System Safety and Performance Post-Approval Study"). The study is intended to further support a reasonable assurance that the final finished SetPoint System, with its approved labeling, is safe when used as intended.

Per the Conditions of Approval, SetPoint Medical will also provide information to FDA regarding the non-clinical training and training materials for the SetPoint System, including materials provided to surgeons and supporting surgical/operative staff, prescribers and patients. On-site SetPoint Medical representatives will be present for each surgeon's first five implantation procedures. Specifically, the conditions require SetPoint Medical to submit:

A. The training and training material provided to:
    i. The on-site SetPoint Medical representatives that will be present for each surgeon's first five (5) implantation procedures;
    ii. Surgeons and supporting surgical/operative staff;
    iii. Patients and prescribers regarding charging procedures and identifying when the device is functioning properly;
B. If any involved person is trained without any written materials, a description of the manner in which this training will occur in a real-world context.
C. Documentation of training that includes the date, purpose, method(s), and the name, professional experience and qualifications of SPM representatives and surgical attendees, and performance (e.g., Pass/Fail, Complete/Incomplete) of surgical attendees.

D. Animal Studies

SetPoint performed a GLP animal study to confirm device readiness for first clinical use. In addition, two other GLP animal studies were conducted to assess the performance of different stimulation configurations and evaluate the local tissue responses following electrocautery.

Animal study to support the first clinical use

This preclinical study was conducted in 16 canines over a 6-month period. The primary objective of this study was to evaluate the safety of the SetPoint System in a chronic canine model. The secondary objective was to evaluate the safety of explanting the device in a chronic canine model. See **Table 5** below.

Table 5: GLP Preclinical Study (111-20) of the Device Design, Conducted to Support First Clinical Use

Study #	Animal Model (N)	Stimulation Parameters Evaluated	Study Duration*	Summary of Goals	Key Findings
Study 111-20	Canines (N=16)	Output current based on OCE (output current escalation) procedure; Pulse width; Pulse frequency	Cohort A: 4 weeks; Cohort B: 12 weeks; Cohort C: 24 weeks;	• Evaluate the safety of the System in a chronic canine model; and • Evaluate the safety of the surgical explant procedure	• This study successfully evaluated the safety of the SetPoint System and the safety of explanting the Implant in a chronic canine model. • There were no adverse events, abnormal gross

Study #	Animal Model (N)	Stimulation Parameters Evaluated	Study Duration*	Summary of Goals	Key Findings
			Cohort D: 12 weeks**		pathology, arrhythmias, or histopathological adverse reactions attributed to the device or stimulation of the vagus nerve.

* Day 0 = First day of stimulation, after approximately 2 weeks of healing following the implantation procedure.
** After 6 weeks of active stimulation, the animals underwent a survival explantation procedure. Per protocol, animals in Cohort D were to be survived for a *minimum* of 4 additional weeks of post-explant healing. The animals were survived for 5 additional weeks of post-explant healing and then euthanized.

This study successfully evaluated the safety of the SetPoint System and the safety of explanting the Implant in a chronic model. There were no adverse events, abnormal gross pathology, arrhythmias, or histopathological adverse reactions attributed to the test article.

Animal study to assess the performance of stimulation

This acute GLP canine study was to compare the neurophysiological and cardiac effects of vagus nerve stimulation via the Pod-secured Implant by measuring evoked compound action potentials in the vagus nerve distally, laryngeal muscle activation, and heart rate. Three canines, two females and one male, were included in the study. Results of this study supported the insulation effect of the Pod and demonstrated that switching polarity of stimulation between two electrodes did not affect the nerve activation.

Animal study to evaluate electrocautery

This GLP animal study assessed the performance and local tissue response to the Implant following exposure to electrocautery in 8 healthy canines. Four (2 males and 2 females) were treated with monopolar electrocautery (30 W, 3 times, at 1 cm from the implant) and the other four animals were treated with bipolar electrocautery (25 W, 3 times for 0.5 to 1 second at approximately 1 cm from the implant). Animals were euthanized for histology at 42 days post implantation. Compared to animals with implantation but without electrocautery, more severe fibrosis and neovascularization in the perineural connective tissue were observed. No significant findings were noted involving the nerve fiber other than slightly higher loss of axonal density. Based on the animal testing result that showed more substantial fibrosis and neovascularization in the perineural connective tissue when electrocautery was used within 1 cm of the implant and nerve, the device labeling indicates a minimum allowable distance of 2 cm between electrocautery and the implant to mitigate the risk of damage to both the implant and the nerve.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

A total of two clinical studies were conducted to assess the safety, feasibility, and efficacy of the SetPoint System, an implantable vagus nerve stimulation (VNS) device for 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). Data from these clinical studies were the basis for the PMA approval decision.

The Feasibility Clinical Study (SPM-008/SPM-011) was a first-in-human clinical study with the SetPoint System. In SPM-008, 14 patients with highly drug refractory RA were

implanted with the SetPoint System (IDE G170231). SPM-008 was a randomized, blinded, sham-controlled clinical study and was conducted at four sites in the U.S. Patient selection for this study was limited to patients who had insufficient responses to at least two biological and/or targeted synthetic (JAKi) disease modifying antirheumatic drugs (bDMARD; tsDMARD), with multiple mechanisms of action (See Table 6 – Key Patient Selection Criteria, below), for whom there were limited or no other therapeutics options.

Additionally, SetPoint performed a clinical study in the U.S. under IDE # G170231 to establish a reasonable assurance of safety and effectiveness 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 one or more biological or targeted synthetic disease modifying antirheumatic drugs (b/tsDMARDs). Data from this clinical study were the basis for the PMA approval decision.

A summary of the clinical studies is presented in **Table 6**.

Table 6: Summary of Clinical Studies

	SPM-008	SPM-011	SPM-020 (RESET-RA)
Study	SPM-008: A Randomized Controlled Study of the Safety and Efficacy of Neurostimulation Using a Vagus Nerve Stimulation Device in Patients with Rheumatoid Arthritis	SPM-011: Long Term Extension Study of the Safety and Efficacy of Neurostimulation Using a Vagus Nerve Stimulation Device in Patients with Rheumatoid Arthritis	An operationally seamless, 2-stage, randomized, sham controlled, double-blind, multicenter, pivotal study with a 12-week follow-up for the primary effectiveness 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.
Key Patient Selection Criteria	• Adult-onset RA as defined by the 2010 ACR/EULAR (European League Against Rheumatism) classification criteria (Aletaha, 2010); • ≥ 4/28 tender and swollen joints and CDAI (Clinical Disease Activity Score) score > 10; and • Failed ≥ 2 bDMARDs and/or new tsDMARDs (JAKi) for ≥ 3 months with insufficient or loss of efficacy or intolerance of treatment.		• Moderate to severe RA, defined as at least 4/28 tender and 4/28 swollen joints • Demonstrated an inadequate response, loss of response, or intolerance to 1 or more biologic or targeted synthetic DMARDs, administered in accordance with their labels
Device	SetPoint NCAP System (also referred to as the SetPoint System)		SetPoint System
Study Site Locations (Number of Sites, N)	United States (N=4)		United States (N=41)
Number of Patients (N)	14 All patients from SPM-008 opted to participate in the long-term extension study SPM-011.		242
Follow-Up Length	12 weeks	93 months	264 weeks
Key Results	Results of this first-in-human Feasibility Study in highly drug refractory RA patients with active		The study met its primary effectiveness endpoint of a

	SPM-008	SPM-011	SPM-020 (RESET-RA)
	moderate to severe disease established the safety of implantation of the SetPoint Implant and active stimulation. Because this was the first clinical use of the SetPoint System, at FDA's request, SetPoint limited patient recruitment in this study to only highly drug refractory patients who had insufficient responses to multiple biologic and/or JAK inhibiting agents, representing multiple mechanisms of action, for whom there were no other therapeutics options. 50% of these highly drug refractory patients receiving VNS with the SetPoint System showed clinically meaningful improvements within 12 weeks of starting stimulation therapy. Long-term safety, device performance, and clinical improvements have been maintained throughout SPM-011, through 60 months. Follow-up is ongoing. Publication: Genovese MC, Gaylis NB, Sikes D, et al. Safety and efficacy of neurostimulation with a miniaturized vagus nerve stimulation device in patients with multidrug-refractory rheumatoid arthritis: a two-stage multicentre, randomised pilot study. *Lancet Rheumatol*. 2020;2(9):e527-e538.		statistically significant difference between treatment and control groups in the proportion of patients achieving an American College of Rheumatology 20% response (ACR20) at Week 12 from baseline on the day of informed consent. Effectiveness was demonstrated by a 35% ACR20 response rate at Week 12 in the treatment arm vs. a 24% response in the control arm (p-value = 0.0209). Effectiveness observed during the blinded evaluation phase was observed to improved further between Week 12 and Week 24 and remained stable and consistent through Week 48. Across all pre-specified endpoints, the 12 Week and longer-term data demonstrated that patients have reduction in disease activity and improved functional disability. The device-related serious adverse event (SAE) rate was 1.6% for events associated with the implantation or explantation procedure (i.e., there were no serious adverse device effects (SADEs) after Week 12 attributed to stimulation or the device. The data support that the SetPoint System for the treatment of moderate-to-severe RA provides probable safety and effectiveness and the benefits outweigh the risks.

RESET-RA Pivotal Clinical Study (SPM-020)

A. Study Design

Patients were treated between 27 January 2021 (first patient implanted with the device) and 2 February 2024 (last patient implanted with the device). Dates of first randomization and last Week 12 visit are shown below.

First Randomization Day 0, about 14-21 days after Implant Procedure	**Last Week 12 visit** primary/secondary endpoints	**Last Week 48 visit** open-label outcomes
22 February 2021	16 May 2024	03 February 2025

The database for this PMA reflected data collected through 10 March 2025 and included 242 patients in the Intent-to-Treat (ITT) population. There were 41 investigational sites.

The RESET-RA Study was a prospective, multicenter, randomized, double-blinded, sham-controlled, pivotal clinical study comparing the active stimulation with SetPoint System (treatment) to sham (control, no stimulation) to evaluate safety and effectiveness. The study consisted of two stages, with Stage 1 enrolling 60 randomized subjects at up to 25 study centers, and Stage 2 increasing enrollment up to 190 randomized subjects at up to 45 study centers (including those from Stage 1). Enrollment was paused for 6 months after enrolling the last subject into Stage 1 to allow completion of Week 12 data collection and comparative data readouts for Stage 1 subjects. Blinding was maintained until all patients completed Week 12 assessments, and the dataset for primary analysis was locked. The Week 12 assessments were 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.

The primary effectiveness endpoint was the difference between treatment and control groups in the proportion of patients achieving the ACR20 response at Week 12 from baseline on the day of informed consent. The primary effectiveness analysis was performed on the ITT population using pooled data from Stage 1 and 2. The hypothesis of interest was:

H_0: $p_t - p_c <= 0$

H_1: $p_t - p_c > 0$

where p_t is the response rate in treatment group and p_c is the response rate in control group.

The study tested the null hypothesis (H_0) that the treatment group response rate is less than or equal to the control group response rate in the proportion of patients achieving ACR20 response at Week 12 from baseline on the day of informed consent versus the alternative hypothesis (H_1) that treatment group response rate exceeds the control group response rate. The study was considered successful if there is a statistically significant improvement in the proportion of patients with ACR20 response in favor of the SetPoint System at a one-sided alpha of 0.025.

To support labeling claims, a subset of secondary endpoints was identified and analyzed using appropriate methods for controlling for family-wise type-1 error rate (FWER).

Sample Size Calculation

The sample size was calculated based on an estimated 60% response rate at Week 12 in the treatment group and 30% response rate at Week 12 in the control group. A sample size of 250 randomized patients, 125 in each group, offered 96% power to detect a difference of 30% at the one-sided alpha of 0.025. If the true response rates were 50% in the treatment and 30% in the control group, the sample size of 250 patients would have 77% power to detect a difference of 20% at the one-sided alpha of 0.025. Power calculations were also considered for the scenario in which enrollment ended at 240 patients. The decrease in power was < 1% for all scenarios and most often < 0.5%.

Core Labs and Independent Evaluators

Two core labs provided independent, blinded evaluations of Magnetic Resonance Imaging (MRI) assessments and central lab service. Vendors are shown below.

Spire Sciences Inc 5314 Boca Marina Circle North Boca Raton, FL 33487	MRI Evaluator
ICON plc 123 Smith Street Farmingdale, NY 11735	Central Lab Services

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) was assembled to ensure safety, compliance, and proper clinical study monitoring. The DMC was responsible for safeguarding the interests of study patients, assessing the safety and effectiveness of the interventions during the trial, and for ongoing monitoring of the overall conduct of the study.

The DMC met on a regular basis and was responsible for making recommendations about stopping or continuing the study based on their ongoing review of cumulative safety and effectiveness data. To date the DMC has consistently recommended that the study continue as planned without any significant alterations, changes, or interruptions.

The DMC was comprised of a DMC Chair (Rheumatologist), DMC Biostatistician, DMC Clinician – Neurosurgeon, DMC Clinician – Otolaryngologist and Head & Neck Surgeon, Independent Biostatistician (non-voting).

Treatment and Control Groups

Starting with consent and screening, the implant procedure was completed within 30 days for all patients, followed by randomization (Day 0) about 2-3 weeks after implant to allow for healing of the incision site. Randomization was 1:1 to either active stimulation (treatment) or non-active stimulation (control or sham). Following the Week 12 assessments, all patients were offered to have their Implants turned on to receive active stimulation (treatment). Blinding was maintained until the last patient enrolled completed the Week 12 assessment.

1. Clinical Inclusion and Exclusion Criteria

   Patients enrolled in the RESET-RA clinical study were adults (22-75 years of age, inclusive) with moderately to severely active RA, despite ongoing treatment with a conventional synthetic DMARD (csDMARD), who had an inadequate response, loss of response, or intolerance to 1 or more biologic or targeted synthetic DMARDs (b/tsDMARDs).

   Enrollment was limited to patients who met the following key inclusion criteria:

   - 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.

Patients were not permitted to enroll in the RESET-RA clinical study if they met any of the following key exclusion criteria:

- 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 or allergy to MRI contrast agents and/or unable to perform MRI

2. Follow-up Schedule

Preoperatively, the Informed Consent and Screening (Baseline) assessments listed in **Table 7** were performed up to 30 days prior to the implant procedure. Postoperatively, the objective parameters measured during the study included all assessments shown in **Table 7** and **Table 8** below. After completing Week 12, all patients had their devices re-registered and set to "active stimulation" and titration repeated (done to maintain blind of the original treatment assignments). This action marked crossover and start of open label with long-term follow-up planned up to Week 264 (**Table 8**). Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

Table 7: Schedule of Assessments, Informed Consent to Week 12 (Primary Endpoint)

Assessment	**Informed Consent & Screening** (Baseline)	**Enrollment & Implant Procedure** (≤ 30d post-Informed Consent)	**Post-Surgical Clearance** (14-21d post-Implant Procedure)	**Day 0** (Randomization & Initiation of Stimulation) (14-21d post-Implant Procedure)	**Week 4** (28 ± 3d[2])	**Week 8** (56 ± 5d[2])	**Week 12** (Primary Endpoint & One-way Crossover) (84 ± 7d[2])
Informed consent	X*						
Vital signs	X*			X			X
Physical exam and medical history	X*						
Pregnancy test (childbearing female)	X*	X	X	X	X	X	X
RA disease activity assessments[1]	X*			X	X	X	X
RA prior and current medication	X*						

Assessment	**Informed Consent & Screening** (Baseline)	**Enrollment & Implant Procedure** (≤ 30d post-Informed Consent)	**Post-Surgical Clearance** (14-21d post-Implant Procedure)	**Day 0** (Randomization & Initiation of Stimulation) (14-21d post-Implant Procedure)	**Week 4** (28 ± 3d[2])	**Week 8** (56 ± 5d[2])	**Week 12** (Primary Endpoint & One-way Crossover) (84 ± 7d[2])
Energizer [Charger] fit test	X*						
SF-36 & EQ-5D-5L questionnaires	X			X	X	X	X
Blood collection (RF, ACPA, eGFR)	X						
Blood collection (CBC, biomarkers)	X			X	X	X	X
Hand MRI	X						X
12-lead ECG	X						X
X-ray cervical spine	X						
Surgical clearance	X		X				
Implant procedure in operating room		X					
Randomization				X			
Patient training on the use of Energizer [Charger]				X			
Device check & dose titration				X			X [3]
Device check & dose adjustment if needed					X	X	
Blinding assessment [4]					X		X

Abbreviations: ACPA, anti-citrullinated protein antibodies; CBC, complete blood count; d, day; EGA, evaluator's global assessment; eGFR: estimated glomerular filtration rate; HAQ-DI, Health Assessment Questionnaire Disability Index; hsCRP, high-sensitivity C-reactive protein; MRI, magnetic resonance imaging; RA, rheumatoid arthritis; RF, rheumatoid factor; SGA, patient's global assessment; SJC, swollen joint count; TJC, tender joint count

* Screening assessments that must be conducted on the day of informed consent to determine patient's initial eligibility and baseline values for the primary and key secondary efficacy endpoints.

[1] RA disease activity assessments include: HAQ-DI, SGA, patient's pain assessment, TJC28, SJC28, EGA, and hsCRP. Patients must have ≥ 4TJC28 and ≥ 4SJC28 at consent to be eligible.

[2] From Day 0 (randomization).

[3] Dose titration is not performed if patient and Co-PI Rheumatologist decide that patient should not receive active stimulation in open-label, long-term follow-up period.

[4] Blinding assessments are completed by the patient, Joint Evaluator and Co-PI Rheumatologist.

Table 8: Schedule of Assessments, Long-Term Follow-Up

Assessment	**Week 24**	**Week 36**	**Week 48**	**Week 60**	**Week 72**	**Week 84**	**Week 96**	**Week 108**	**Week 120**	**Week 132**	**Week 144**	**Week 156**	**Week 168**	**Week 180**	**Week 192**	**Week 204 thru 264 (visits every**
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (childbearing female)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RA disease activity assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SF-36 & EQ-5D-5L questionnaires	X		X				X				X				X	
Satisfaction questionnaire	X															
Blood collection (CBC)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood collection (biomarkers)	X															
Hand MRI	X															
12-lead ECG	X		X				X				X				X	
Device check & dose titration																
Device check & dose adjustment if needed	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Device deficiency reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Clinical Endpoints

With regard to safety, the risks of the device were based on nonclinical laboratory data as well as data collected in the RESET-RA clinical study. Safety of the SetPoint System was reported based on adverse events observed during the RESET-RA study. Adverse events were reported by the study doctor as related to either the implantation or explantation procedure, the device, stimulation therapy, or Charger associated with the SetPoint System. Additionally, adverse events were assessed by the study doctor as serious or non-serious as well as anticipated or unanticipated.

With regard to effectiveness, the difference between treatment and control groups in the proportion of patients who achieved the American College of Rheumatology 20% response (ACR20) at Week 12 was the primary effectiveness endpoint.[1] The primary endpoint was further supported by additional efficacy measurements as secondary endpoints and exploratory endpoints.

Primary Endpoint

The ACR20 is a common primary endpoint in randomized controlled trials (RCTs) to evaluate treatment in RA. ACR20 is a dichotomous composite endpoint indicating the proportion of patients with at least 20 percent improvement in the number of tender and swollen joints, and in three out of the remaining five ACR core-set measures: patient pain, patient global assessment of disease, evaluator global assessment of disease, physical functioning assessment (Health Assessment Questionnaire-Disability Index [HAQ-DI]), and acute phase reactants (i.e., hsCRP).[1,2]

The core set of measures included in the ACR response criteria was established through a consensus process of clinical experts. Individual criteria were selected based on their construct validity, face validity, content validity, criterion validity, and discriminant validity. When considering the ability of an outcome measure to detect change, pain assessments, global assessments, tender and swollen joint counts, and HAQ scores all had strong discriminant validity.[2] The core-set of measures are briefly described below:

- Tender Joint Count 28 (TJC280 and Swollen Joint Count 28 (SJC28):
  A total of 28 joints were scored for presence or absence of tenderness or pain and swelling in: the shoulder (2), elbow (2), wrist (2), knee (2), and fingers (2 in each finger and thumb knuckle and second finger joint, 10 per hand or 20 total). All joint assessments were performed by an independent, blinded Joint Evaluator with appropriate training and experience. Each patient was assessed by the same Joint Evaluator throughout their participation in the study. Joints that were replaced or injected with intra-articular steroids during the study are considered unevaluable.

- Patient's Pain Assessment:
  Patient completed an assessment of the severity of their RA-related pain by marking a numerical rating scale on a paper form. The scale ranged from 0 (no pain) to 10 (worst pain imaginable).

- Patient's Global Assessment (PGA):
  Patient completed a global assessment of their RA disease activity by marking a

numerical rating scale on a paper form. The scale ranged from 0 (inactive) to 10 (very active). This assessment was completed independently from Joint Evaluator's assessment.

- Evaluator's Global Assessment (EGA):
  After performing joint assessments, the same Joint Evaluator conducted a global assessment of the patient's RA activity by marking a numerical rating scale on a paper form. The scale ranged from 0 (inactive) to 10 (very active). Each patient was assessed by the same Joint Evaluator throughout their participation in the study. The Joint Evaluator completed their assessments without knowledge of SGA.

- High-sensitivity C-reactive protein (hsCRP):
  Blood samples for hsCRP were collected using sampling kits and shipped at room temperature to a central laboratory for analysis, Serum concentration of hsCRP (mg/L) were determined by immunoturbidimetric assay.

- Health Assessment Questionnaire Disability Index (HAQ-DI):
  A self-reported questionnaire that assesses functional ability in individuals. It evaluates the difficulty a patient experiences in performing activities of daily living across eight categories: dressing, arising, eating walking, hygiene, reach, grip, and common activities. The HAQ–Disability Index (HAQ-DI) is a comprehensive measure of the patient's perception of functional status and has been widely validated in RA.[3,4] Patients completed the HAQ-DI questionnaire using a validated paper form in their language (English or Spanish). There are 20 questions in eight categories to assess a patient's physical functional status. For each question, there is a 4-level response set that is scored from 0 (without any difficulty) to 3 (unable to do). The eight category scores are averaged into an overall HAQ-DI score on a scale from zero (no disability) to three (completely disabled). Observational studies and RCTs have demonstrated that the HAQ-DI demonstrates face validity, content validity, construct validity, predictive validity, and discriminant validity.[3,4]

Secondary Endpoints

ACR20 response from Day 0

A patient achieved ACR20 response when this patient experienced a ≥ 20% improvement at Week 12 from the post-surgical baseline at Day 0 in TJC28 and SJC28 and 3 out of 5 ACR core measures and follows the same general and statistical analyses as for ACR20 response at Week 12 from baseline on the day of informed consent (primary endpoint).

DAS28-CRP response (MCID)

The DAS28-CRP (28-joint Disease Activity Score using C-reactive protein) is a validated measure for assessing disease activity in RA.[5]

The DAS28-CRP score is a composite index providing a measure of disease activity, comprising TJC28 (tender joint count for 28 joints), SJC28 (swollen joint count for

28 joints), SGA (subjective global assessment), and hsCRP (high-sensitivity C-reactive protein in mg/L). A total score ranges from 0 to 10 and is computed as follows:

*DAS28-CRP = 0.56 * sqrt(TJC28) + 0.28 * sqrt(SJC28) + 0.36 * ln(CRP+1) + 0.014 * SGA + 0.96*

A DAS28-CRP score reduction by at least 1.2 from baseline on the day of inform consent to Week 12 represented the MCID response.

DAS28-CRP good/moderate EULAR response

The European League Against Rheumatism (EULAR) recommended that the clinical implications of the DAS28 score (such as good response, moderate response, or no response) be determined based on the baseline DAS28 scores.[6]

DAS28-CRP EULAR response at Week 12 was defined based on the combination of the current DAS28-CRP score and its improvement relative to baseline on the day of inform consent as illustrated in **Table 9**.

Table 9: EULAR Response Criteria

DAS28-CRP Score Week 12	DAS28-CRP Score Decrease from Baseline Value		
	> 1.2	**> 0.6 to ≤ 1.2**	**≤ 0.6**
≤ 3.2	Good response	Moderate response	No response
> 3.2 to ≤ 5.1	Moderate response	Moderate response	No response
> 5.1	Moderate response	No response	No response

A patient was considered having a moderate treatment response at Week 12 if:

- DAS28-CRP score decreased from baseline to Week 12 by > 0.6 and ≤ 1.2, and the DAS28-CRP score at Week 12 was ≤ 5.1; or
- DAS28-CRP score decreased from baseline to Week 12 by > 1.2, and the DAS28-CRP score at Week 12 was > 3.2.

A patient was considered having a good treatment response at Week 12 if:

- DAS28-CRP score decreased from baseline to Week 12 by > 1.2 and the DAS28-CRP score at Week 12 was ≤ 3.2.

If the post-baseline DAS28-CRP score was missing, then the corresponding EULAR category was missing.

HAQ-DI response (MCID)

The HAQ–Disability Index (HAQ-DI) is a comprehensive measure of the patient's perception of functional status and has been widely validated in RA.[4,5] Patients completed the HAQ-DI questionnaire using a validated paper form in their language (English or Spanish). There are 20 questions in eight categories to assess a patient's physical functional status: dressing, arising, eating, walking, hygiene, reach, grip, and common activities. Each functional area contains at least 2 questions. For each question, there is a 4-level response set that is scored from 0 (without any difficulty)

to 3 (unable to do). If aids or devices or physical assistance are used for a specific functional area, and the maximum response of this functional area is 0 or 1, the according value is increased to a score of 2. The highest response within each functional area determines the score of that specific functional area. If no questions within a given functional area were answered, no score was provided for that category (even if answers on aids or equipment are available). The eight category scores are averaged into an overall HAQ-DI score on a scale from zero (no disability) to three (completely disabled). HAQ-DI score was only calculated if there were at least 6 functional area scores available. Observational studies and RCTs have demonstrated that the HAQ-DI demonstrates face validity, content validity, construct validity, predictive validity, and discriminant validity.[5,] The minimal clinically important difference (MCID) in HAQ-DI reflecting a meaningful improvement in physical function is a decrease in score of 0.22, derived from correlations with global assessments of disease activity in multiple randomized controlled trials and longitudinal case series.[3]

Exploratory Endpoints

CDAI low disease activity or remission

The Clinical Disease Activity Index (CDAI) is a validated composite measure that is widely used in clinical practice to assess disease activity level in rheumatoid arthritis in patients. The score is based on 4 items:

- TJC28
- SJC28
- SGA
- EGA

The CDAI score is calculated as follows and ranges from 0 to 76: CDAI = TJC28 + SJC28 + SGA + EGA

The CDAI score corresponds to the current RA activity:

- 0 to ≤ 2.8 Remission
- > 2.8 to ≤ 10 Low disease activity (LDA)
- > 10 to ≤ 22 Moderate disease activity
- > 22 High disease activity

DAS-28 CRP low disease activity or remission

The DAS28-CRP score corresponds to the current RA activity as follows:

- 0 to < 2.6 Remission
- 2.6 to < 3.2 LDA
- 3.2 to ≤ 5.1 Moderate activity
- > 5.1 High activity

Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS)[7-11]

A contrast-enhanced MRI of one hand identified by the rheumatologist to be clinically most severe was ordered by the rheumatology site and acquired at an MRI facility that was selected and qualified to perform this procedure. The MRI images

were acquired before and after intravenous administration of gadolinium-based contrast to maximize sensitivity and specificity for inflammation.

RAMRIS was evaluated at baseline, Week 12, and then Week 24 (after one-way crossover) as an exploratory endpoint. RAMRIS is a standardized method for MRI acquisition of the hand and wrist to assess joint pathology by definitions and a scoring system for semiquantitative evaluation per:

- Synovitis: 8 joints each scored on a scale from 0 (normal) to 3 (severe), resulting in a total score from 0 to 24.
- Bone erosion: 25 bones each scored on a scale from 0 to 10, resulting in a total score from 0 to 250. Change by > 0.5 represents disease progression.
- Osteitis: 25 bones each scored on a scale from 0 to 3, resulting in a total score from 0 to 75.

RAMRIS synovitis, bone erosion, and osteitis score changes from baseline, Week 12 and Week 24 were evaluated as an exploratory endpoint. The percentage of patients exhibiting a progression in bone erosions (increase in erosion score of > 0.5 compared to baseline) was also prespecified. Subgroup analysis was performed on patients that had only failed one prior b/tsDMARD and those with an erosive phenotype. Patients meeting the subgroup criteria for having an erosive phenotype had a baseline synovitis score of 2 or more on any joint; or, if none of the joints score greater than 2, had at least 4 joints with a score of 1 at baseline; or had any joint with osteitis (score of 1 or more) at baseline.

The same hand was imaged using the same MRI scanner and coil at Screening, Week 12, and Week 24 for a given patient. Only 1.5 and 3.0 Tesla (1.5T and 3.0T) whole-body scanners and transmit-receive (Tx/Rx) coils, ideally knee coils, were acceptable for this study. In vitro testing of Implant and Pod passed standard testing for safe use in 1.5T and 3.0T MRI studies. Safe scanning parameters are provided in the SetPoint Medical Surgeon, Prescriber and Patient Manuals.
MRI images were transmitted to the MRI central laboratory for quality check, reading and quantification. Images were scored centrally by two independent radiologists blinded to treatment allocation, clinical information and the order (study assessment) in which the images were acquired. Scores for each bone/joint were calculated as the average of the score provided by each of the two readers.

The smallest detectable change (SDC) was calculated for each of the joint pathologies to assess whether a patient experienced a change beyond measurement error.[10] Changes below the smallest detectable change (-SDC) reflect improvement in RAMRIS subscores; changes above the smallest detectable change (+SDC) reflect worsening.

Therapy Persistence

Therapy persistence refers to the length of time a study patient continued to use the study therapy. Persistence was assessed in several ways:

- Use of the SetPoint System without addition of a b/tsDMARD, additional csDMARD and/or steroid

- Use of the SetPoint System with the addition of a b/tsDMARD
- Use of the Setpoint System with an additional csDMARD or steroid

Patient Satisfaction

Patient satisfaction with the SetPoint System for treatment of RA was assessed at Week 24 (after all participants had received at least 12 weeks of study therapy) using five-point Likert rating scale:

- Very dissatisfied
- Somewhat dissatisfied
- Neither satisfied nor dissatisfied
- Somewhat satisfied
- Very satisfied

Additionally, patients were asked a question about whether they would recommend the SetPoint System to family and friends.

B. Accountability of PMA Cohort

At the time of database lock, 242 patients were implanted in the RESET-RA clinical study at 41 sites, all in the United States, with 240 (99.2%) of patients available for analysis at primary endpoint analysis at Week 12 after randomization. Patient accountability is shown in **Figure 7** below.

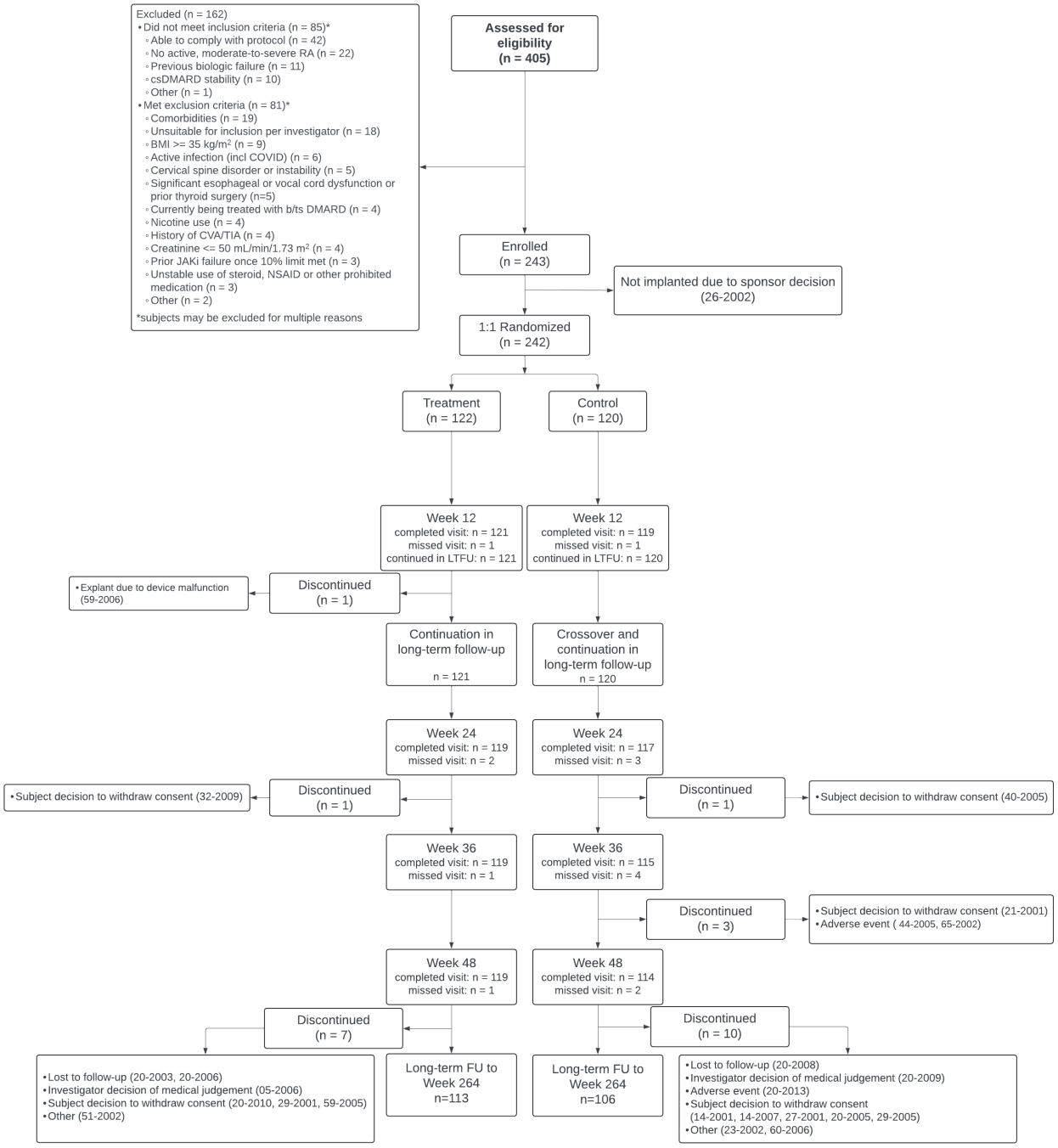

Figure 7: Patient Accountability

C. Study Population Demographics and Baseline Parameters

Enrollment in the RESET-RA clinical study was entirely from study sites in the U.S. (i.e., no study sites outside the U.S. participated in RESET-RA), Therefore, the demographics for the study population are typical for what would be expected in an RA study performed in the U.S. and representative of a U.S. patient population with RA. The prevalence of RA is 3 times higher in women than men, the incidence is 4-5 times higher below the age of 50, but above 60-70 years the female/male ratio is only about 2.[12]

Demographics for the ITT cohort are reported in **Table 10** below. The ITT population was predominately female (86%), with a higher proportion of males in the treatment group (19.7% treatment vs. control 8.3%). Mean age was 55.7 years at time of consent.

By race and ethnicity, most patients were White (80.6%), and representation by Hispanic or Latino was 18.6%. On average, patients were overweight with mean BMI 30.3 kg/m^2. In general, demographics and baseline characteristics were balanced between the treatment and control group, with no differences identified that would have an unexpectedly material impact on clinical results.

Table 10: Demographics (ITT Population)

	Treatment (N=122)	Control (N=120)	All (N=242)
Age (years)			
I. Mean (SD)	55.8 (10.28)	55.5 (10.49)	55.7 (10.36)
II. Median	57.0	56.5	57.0
III. Min, Max	25, 75	30, 75	25, 75
Sex			
IV. Male	24 (19.7%)	10 (8.3%)	34 (14.0%)
V. Female	98 (80.3%)	110 (91.7%)	208 (86.0%)
Ethnicity			
VI. Hispanic or Latino	23 (18.9%)	22 (18.3%)	45 (18.6%)
VII. Not Hispanic or Latino	98 (80.3%)	95 (79.2%)	193 (79.8%)
VIII. Not disclosed	1 (0.8%)	3 (2.5%)	4 (1.7%)
Race [1]			
IX. American Indian or Alaska Native	1 (0.8%)	0	1 (0.4%)
X. Asian	4 (3.3%)	5 (4.2%)	9 (3.7%)
XI. Black or African American	10 (8.2%)	12 (10.0%)	22 (9.1%)
XII. Native Hawaiian or other Pacific Islander	0	1 (0.8%)	1 (0.4%)
XIII. White	102 (83.6%)	93 (77.5%)	195 (80.6%)
XIV. Other	5 (4.1%)	9 (7.5%)	14 (5.8%)
Body Mass Index (kg/m^2)			
XV. Mean (SD)	30.7 (7.25)	29.8 (6.71)	30.3 (6.98)
XVI. Median	29.6	28.7	29.2
XVII. 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			

Baseline RA duration, disease activity, and serology are shown in **Table 11**.

Table 11: Baseline RA Duration, Disease Activity, Serology (ITT Population)

	Treatment (N=122)	Control (N=120)	All (N=242)
RA duration (years)			
I. Mean (SD)	13.0 (10.59)	11.8 (10.45)	12.4 (10.52)
II. Median	10.0	8.5	9.2
III. Min, Max	0.1, 55.5	0.7, 51.8	0.1, 55.5
CDAI score			
IV. Mean (SD)	36.1 (12.60)	38.2 (12.75)	37.1 (12.69)
V. Median	33.8	37.1	35.1
VI. Min, Max	13.5, 73.5	16.5, 74.0	13.5, 74.0
DAS28-CRP score			
VII. Mean (SD)	5.3 (0.91)	5.4 (0.96)	5.3 (0.93)
VIII. Median	5.2	5.3	5.3
IX. Min, Max	3.4, 7.6	3.0, 7.9	3.0, 7.9
RF			
X. Negative	73 (59.8%)	64 (53.3%)	137 (56.6%)
XI. Positive	49 (40.2%)	56 (46.7%)	105 (43.4%)
XII. NA	0	0	0
ACPA			
XIII. Negative	57 (46.7%)	61 (50.8%)	118 (48.8%)
XIV. Positive	61 (50.0%)	59 (49.2%)	120 (49.6%)
XV. NA	4 (3.3%)	0	4 (1.7%)
Serology			
XVI. Negative	56 (45.9%)	54 (45.0%)	110 (45.5%)
XVII. Positive	62 (50.8%)	66 (55.0%)	128 (52.9%)
XVIII. NA	4 (3.3%)	0	4 (1.7%)

Abbreviations: RA, rheumatoid arthritis, ACPA, anti-citrullinated protein antibodies; CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score 28 using C-reactive protein; ITT, intent to treat; RF, Rheumatoid factor; SD, standard deviation

ACR components measured at baseline (day of consent) were comparable between treatment and control for tender and swollen joint counts, HAQ-DI score, pain score, subject global assessment, evaluator global assessment, and hsCRP (high-sensitivity CRP). ACR components at baseline are provided in **Table 12**.

Table 12: Baseline ACR Components (ITT Population)

	Treatment (N=122)	Control (N=120)	All (N=242)
TJC (out of 28 joints)			
I. Mean (SD)	14.1 (6.94)	15.0 (7.26)	14.6 (7.10)
II. Median	12.4	14.0	14.0

	Treatment (N=122)	Control (N=120)	All (N=242)
III. Min, Max	4.0, 28.0	4.0, 28.0	4.0, 28.0
SJC (out of 28 joints)			
IV. Mean (SD)	9.6 (5.46)	10.5 (4.98)	10.0 (5.23)
V. Median	7.8	9.2	9.0
VI. Min, Max	4.0, 28.0	4.0, 28.0	4.0, 28.0
HAQ-DI score			
VII. Mean (SD)	1.4 (0.59)	1.3 (0.61)	1.4 (0.60)
VIII. Median	1.4	1.4	1.4
IX. Min, Max	0.1, 2.8	0.0, 2.9	0.0, 2.9
Pain (per subject)			
X. Mean (SD)	5.5 (2.00)	5.7 (2.23)	5.6 (2.12)
XI. Median	5.5	6.0	6.0
XII. Min, Max	1.0, 10.0	1.0, 10.0	1.0, 10.0
SGA			
XIII. Mean (SD)	6.2 (2.07)	6.0 (2.25)	6.1 (2.16)
XIV. Median	6.0	6.0	6.0
XV. Min, Max	2.0, 10.0	1.0, 10.0	1.0, 10.0
EGA			
XVI. Mean (SD)	6.3 (1.88)	6.7 (1.72)	6.5 (1.80)
XVII. Median	6.3	7.0	7.0
XVIII. Min, Max	1.5, 10.0	2.0, 10.0	1.5, 10.0
hsCRP (mg/L)			
XIX. Mean (SD)	8.41 (12.338)	8.01 (12.762)	8.21 (12.526)
XX. Median	3.87	2.63	3.08
XXI. Min, Max	0.15, 69.76	0.09, 85.48	0.09, 85.48

Abbreviations: TJC28, tender joint count; SJC, swollen joint count; HAQ-DI, health assessment questionnaire-disability index; SGA, subject global assessment; EGA, evaluator global assessment; hsCRP, high-sensitivity C-reactive protein

Medical history of prior biological and targeted synthetic DMARDs (b/tsDMARDs) is presented in **Table 13**. 43% of the study population met the EULAR criteria for difficult-to-treat (D2T) with available drug therapies.[6]

Table 13: Number of Prior b/tsDMARDs (ITT Population)

	Treatment (N=122)	Control (N=120)	All (N=242)
Prior b/ts DMARDs			
I. Mean (SD)	2.5 (1.98)	2.7 (1.87)	2.6 (1.92)
II. Median	2.0	2.0	2.0
III. Min, Max	1.0, 12.0	1.0, 10.0	1.0, 12.0
Number of prior b/tsDMARDs			

	Treatment (N=122)	Control (N=120)	All (N=242)
IV. 0	0	0	0
V. 1	52 (42.6%)	42 (35.0%)	94 (38.8%)
VI. 2	25 (20.5%)	28 (23.3%)	53 (21.9%)
VII. 3	15 (12.3%)	16 (13.3%)	31 (12.8%)
VIII. 4	15 (12.3%)	15 (12.5%)	30 (12.4%)
IX. 5	7 (5.7%)	8 (6.7%)	15 (6.2%)
X. 6	2 (1.6%)	5 (4.2%)	7 (2.9%)
XI. 7	2 (1.6%)	4 (3.3%)	6 (2.5%)
XII. 8	2 (1.6%)	1 (0.8%)	3 (1.2%)
XIII. 9	0	0	0
XIV. 10+	2 (1.6%)	1 (0.8%)	3 (1.2%)
Prior b/tsDMARD by Classification [1]			
XV. Anti-IL-1 agents	0	4 (3.3%)	4 (1.7%)
XVI. Anti-IL-6 agents	27 (22.1%)	28 (23.3%)	55 (22.7%)
XVII. Anti-TNF agents	116 (95.1%)	109 (90.8%)	225 (93.0%)
XVIII. B-cell depleting agents	13 (10.7%)	21 (17.5%)	34 (14.0%)
XIX. JAKi	25 (20.5%)	24 (20.0%)	49 (20.2%)
XX. CTLA4-Ig	32 (26.2%)	36 (30.0%)	68 (28.1%)

Abbreviations: ACPA, anti-citrullinated protein antibodies; b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug; CTLA4-Ig, cytotoxic T-lymphocyte-associated antigen-4 immunoglobulin; IL, interleukin; ITT, intent to treat; JAKi, Janus kinase inhibitor; RA, rheumatoid arthritis; SD, standard deviation; TNF, tumor necrosis factor

[1] Patients could be counted in more than 1 category.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the safety cohort of 243 patients consented. The key safety outcomes for this study are presented below in **Table 14** and **Table 17**. Adverse effects are reported in **Table 14** to **Table 17**.

Adverse Events that occurred in the PMA Clinical Study

Determination of safety for the SetPoint System is based on adverse events observed during the RESET-RA study. Adverse events were reported by the study doctor as related to either the implantation procedure, explantation procedure (if applicable), device, stimulation or Charger associated with the SetPoint System.

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 (overall, 16% of patients). Most AEs were related to the implantation procedure. No events resulted in discontinuation of a patient during this period. There were no Unanticipated Adverse Device Effects (UADEs) and no deaths from Screening to Week 12. A total of 4 patients (1.6%) experienced a serious adverse event (SAE) related to the implantation or explantation procedure of the SetPoint System during the period from implantation procedure to Week 12 as summarized in **Table 14**. All (100%) SAEs resolved.

Table 14: Related, Serious AEs from Implantation to Week 12

MedDRA Preferred Term		Treatment (N=122) n (%)	Control (N=120) n (%)	All (N=243) n (%)
Patient with AE		3 (2.5%)	1 (0.8%)	4 (1.6%)
XVIII.	Incision site swelling [1]	1 (0.8%)	0	1 (0.4%)
XIX.	Vocal cord paresis [1]	1 (0.8%)	0	1 (0.4%)
XX.	Dysphonia [1]	0	1 (0.8%)	1 (0.4%)
XXI.	Pharyngeal perforation [2]	1 (0.8%)	0	1 (0.4%)

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).

Non-serious AEs related to the implantation procedure and/or Implant are summarized in **Table 15**. These AEs were generally mild to moderate in severity and anticipated based on the nature of the surgical intervention.

Table 15: Non-Serious AEs Related to Implantation Procedure and/or Implant

MedDRA Preferred Term		Treatment (N=122) n (%)	Control (N=120) n (%)
Patient with AE		17 (13.9%)	22 (18.3%)
I.	Vocal cord paresis	5 (4.1%)	6 (5%)
II.	Dysphonia	4 (3.3%)	3 (2.5%)
III.	Cough	1 (0.8%)	0
IV.	Diarrhea	1 (0.8%)	0
V.	Dysphagia	1 (0.8%)	2 (1.7%)
VI.	Dyspnea	1 (0.8%)	0
VII.	Gastrointestinal complication	1 (0.8%)	0
VIII.	Implant site hypoesthesia	1 (0.8%)	1 (0.8%)

MedDRA Preferred Term	Treatment (N=122) n (%)	Control (N=120) n (%)
IX. Implant site inflammation	1 (0.8%)	1 (0.8%)
X. Implant site swelling	1 (0.8%)	2 (1.7%)
XI. Medical device site swelling	1 (0.8%)	0
XII. Migraine	1 (0.8%)	0
XIII. Postoperative wound infection	1 (0.8%)	0
XIV. Rash	1 (0.8%)	1 (0.8%)
XV. Scar pain	1 (0.8%)	0
XVI. Stitch abscess	1 (0.8%)	0
XVII. Swelling	1 (0.8%)	0
XVIII. Swelling of eyelid	1 (0.8%)	1 (0.8%)
XIX. Application site rash	0	2 (1.7%)
XX. Eyelid ptosis	0	1 (0.8%)
XXI. Headache	0	1 (0.8%)
XXII. Implant site erythema	0	1 (0.8%)
XXIII. Implant site pain	0	2 (1.7%)
XXIV. Oropharyngeal pain	0	1 (0.8%)
XXV. Procedural pain	0	1 (0.8%)
XXVI. Suture related complication	0	1 (0.8%)
XXVII. 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.		

Non-serious vocal cord paresis (VCP), which presented clinically as hoarseness, was the most common procedure-related AE, occurring in 5 patients (4.1%) in the treatment group and 6 patients (5%) in the control group. The procedure-related AEs reported in the study are known to occur in this device class and are consistent with other FDA-approved implantable VNS devices. At last visit or study exit, 90% of the AEs were resolved, and 10% were ongoing.

Stimulation therapy was well-tolerated, with all AEs reported as mild or moderate in severity (**Table 16**). All (100%) non-serious, stimulation-related AEs from randomization to Week 12 resolved.

Table 16: Non-Serious, Stimulation Related AEs from Randomization to Week 12

MedDRA Preferred Term	Treatment (N=122) n (%)	Control [1] (N=120) n (%)	All (N=243) n (%)
Patient with AE	10 (8.2%)	0	10 (4.1%)
XXII. Medical device pain	4 (3.3%)	0	4 (1.6%)
XXIII. Choking sensation	1 (0.8%)	0	1 (0.4%)

MedDRA Preferred Term	Treatment (N=122) n (%)	Control [1] (N=120) n (%)	All (N=243) n (%)
XXIV. Cough	1 (0.8%)	0	1 (0.4%)
XXV. Dysgeusia	1 (0.8%)	0	1 (0.4%)
XXVI. Oropharyngeal pain	1 (0.8%)	0	1 (0.4%)
XXVII. Procedural nausea	1 (0.8%)	0	1 (0.4%)
XXVIII. Retching	1 (0.8%)	0	1 (0.4%)
XXIX. Toothache	1 (0.8%)	0	1 (0.4%)

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] There were 6 AEs classified by the Co-PI Rheumatologist as related to stimulation that were reclassified to "not related" once the database was locked, the study was unblinded, and it was determined the patients experiencing these AEs has been assigned to the control group. This reassignment was done in accordance with the study protocol: CLP-001, Section 15.2.2. The following evets were reclassified:
21-2001, AE #1: "worsening chronic back pain"
25-2002, AE #6: :intermittent lightheadedness"
25-2005, AE #1: "hoarseness"
31-2001, AE #4: "tingling left side of neck"
38-2004, AE #4: "hoarseness/loss of voice"
59—2020, AE #1: "slight headaches, consistent"

Change was only made to the relationship to stimulation. Relationships to implant device, implant procedure, explant procedure, or Energizer [Charger] were not changed.

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. All but 1 (96%) of the non-serious, stimulation related AEs from randomization to Week 12 resolved. The one on-going event is reported as "medical device pain that is very mild but still present; pain is tolerable and not bothersome."

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), 5.0% of patients in the Treatment to Open Label (TOL) population and 5.0% in the Control to Open Label (COL) population experienced an AE related to the implantation procedure or the SetPoint System. None of these were serious. Most were related to stimulation, and mild or moderate severity. These events were dysphonia, implant site pain, muscle spasms, presyncope, temporomandibular joint syndrome, implant site paresthesia, medical device site discomfort, poor quality sleep, and trigeminal neuralgia.

Two patients discontinued treatment due to non-serious, related AEs (abdominal discomfort and implant site inflammation). Time from Week 12 to data cut on March 10, 2025, ranged from 42.6 to 198 weeks, mean was 96.5 weeks.

There were no related serious AEs, Unanticipated Adverse Device Effects (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, shown in **Table 17**. Same as with the period Implantation to Week 12, these AEs were managed by suspending stimulation or adjusting the stimulation strength or time of delivery. All (100%) stimulation related AEs during long-term follow-up resolved.

Table 17: Stimulation Related AEs during Long-Term Follow-Up

MedDRA Preferred Term	TOL (N=121) n (%)	COL (N=120) n (%)
Patient with AE	6 (5.0%)	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%)

[1] Exacerbation of neuralgic symptoms of trigeminal neuralgia.
*Relationship to implant device was also indicated for these events
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.

Explant Summary

At the time of FDA review for the SetPoint System, the Implant was explanted in 14 of the 242 (5.8%) of patients. The average duration between implantation and explant among the 14 patients was 469 days, ranging from 141 to 1364 days. No patients were explanted through Week 12 visit, and 4 Implants were explanted between Week 12 and Week 24 visits. The remainder were explanted after the Week 24 visit. Refer to **Table 18** below.

Table 18: Summary of Device Explantations

Patient ID	Implant Duration (days)	Reason for Explantation	Explantation-Related Adverse Event (Yes/No)
21-2001	294	patient preference	No
29-2001	446	patient preference	No
27-2001	490	patient preference	No
29-2005	562	patient preference	No
32-2009	225	patient preference	No
20-2010	394	patient preference	No
21-2001	294	patient preference	No
29-2001	446	patient preference	No
27-2001	490	patient preference	No

Patient ID	Implant Duration (days)	Reason for Explantation	Explantation-Related Adverse Event (Yes/No)
29-2005	562	patient preference	No
32-2009	225	patient preference	No
20-2010	394	patient preference	No
40-2005	211	patient preference	No
44-2005	248	GI symptoms attributed to stimulation therapy	No
20-2005	831	patient preference	No
65-2002	276	chronic pain at incision site	No
59-2006	141	non-functioning device	Yes
59-2005	457	patient preference	No
20-2013	630	need for radiation therapy in the head and neck due to metastatic squamous cell carcinoma	No
24-2001	1,364	patient preference	No

The adverse event related to a non-functioning device (59-2006) was related to an incorrect method used to identify the location of the implanted device. The intraoperative complication was pharyngeal perforation (repaired intraoperatively, no hospitalization) with postoperative symptoms of hoarseness and difficulty swallowing. At the time of study exit, the pharyngeal perforation and difficulty swallowing had resolved, and hoarseness was improving and determined to be mild and stable.

Discontinuation due to Adverse Events

Three patients reported non-serious, related AEs that resulted in discontinuation.
One patient in the cross-over group reported symptoms of gastrointestinal (GI) upset including nausea, diarrhea, and pain after Week 12, after receiving stimulation for about 3 weeks. She reported there was no change to her gastroesophageal reflux disease (GERD) medication to account for the GI symptoms. This patient elected to have the device explanted and her GI symptoms were reported as resolved after the explant procedure.

The second patient had ongoing complaints of pain, burning, and soreness at the incision site following the implant procedure. Evaluation showed no clear indication for the cause of the pain or the other symptoms. The patient elected to have the device removed, after which all symptoms were resolved.

The third patient was diagnosed with head and neck metastatic squamous cell carcinoma (HNSCC). Per SetPoint System Instructions for Use Surgeon's Manual, radiation treatment is a restricted medical procedure requiring the implant to be turned off or removed, depending on the location of treatment relative to the device. Explantation of the device was deemed appropriate in order for the patient to pursue radiation treatment.

Safety Profile of the Device for the Proposed IFU

The primary risks associated with this vagus nerve stimulator device relate to both the surgical implantation procedure and the stimulation therapy itself. Vocal cord paresis represents a

significant risk due to the device's direct contact with the vagus nerve, which innervates the recurrent laryngeal nerve controlling vocal cord function. This can manifest as hoarseness or complete voice changes that may be temporary or permanent. Additional procedural risks include bleeding, infection at the implant site, nerve damage during surgical placement, and potential adverse reactions to anesthesia. Device-related risks encompass the possibility of inappropriate stimulation parameters causing discomfort, cardiac arrhythmias due to vagal stimulation effects on heart rate, and potential tissue reaction or scarring around the cuff interface. The integrated cuff design avoids the risks associated with implanting both a pulse generator and electrode lead, including potential need for surgical revisions as a result of lead fracture or migration. Related-AEs with the highest frequency were mild-to-moderate vocal cord paresis (VCP) or hoarseness.[19,20] No unanticipated adverse events were observed during the RESET-RA clinical study.

Stimulation was well-tolerated with stimulation therapy lasting a short duration (1 minute, once per day) at a relatively low stimulation strength. If the patient experiences discomfort or other undesired effects, stimulation strength can easily be adjusted.

The integrated cuff design incorporates both the pulse generator and electrodes within a single unit that wraps directly around the vagus nerve. This unified architecture eliminates the need for separate lead wires extending from a remote pulse generator, thereby removing risks associated with lead fracture, migration, or disconnection that could require surgical revision. The self-contained design reduces the number of steps involved in the implantation procedure and reduces the overall surgical footprint within the patient's anatomy.

No device-related SAEs have occurred during long-term follow-up. Non-related AEs were well-balanced between the treatment and control groups, and other safety monitoring (hematology, ECG, vital signs) did not identify any safety concerns with the device or treatment. There have been no reports of serious infections, malignancies or cardiovascular events attributed to the SetPoint System during the clinical study. The Implant and Pod can be safely removed, if needed, during an outpatient procedure, with no damage or trauma to the vagus nerve based on clinical experience to date. No device revisions have been required during long-term follow-up. Lastly, independent clinicians and biostatisticians on the Data Monitoring Committee have not identified safety concerns during their ongoing review of safety data.

In conclusion:

- Related SAE rate was low (1.6%), with zero (0%) related SAEs during long-term follow-up;
- AEs were predominately mild-to-moderate in severity, nonserious, and relatively straightforward to diagnosis and manage;
- No safety concerns have been identified during long-term follow-up, ranging from 42.6 to 198 weeks (mean 96.5 weeks);
- Risks were limited predominately to the implantation procedure;
- Stimulation therapy was well-tolerated; and
- The SetPoint device can be safely removed (if necessary) without damage to the vagus nerve.

2. Effectiveness Results

Primary Endpoint

The analysis of effectiveness was based on an ITT population of 242 patients at the Week 12 assessment. Key effectiveness outcomes are presented in **Table 19**. 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 at Week 24 and longer follow-up periods. 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 19: ACR20 Response at Week 12 from Baseline by Intention-to-treat (ITT)

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 based on the Cochran-Mantel-Haenszel test accounting for stratification. Note: Baseline measured at time of consent; subject imputed as non-responder if rescued prior to Week 12, regardless of treatment assignment; subject imputed as non-responder if missing at Week 12						

Secondary Endpoints

Although not statistically powered for the secondary endpoints, consistent trends in favor of treatment were seen across secondary endpoints after multiplicity adjustment, as shown in **Table 20**.

Table 20: Secondary Efficacy Endpoints at Week 12 – All Patients (ITT)

ACR20 Response at Week 12 from Day 0						
Group	**Total**	**Responder**	**%**	**Difference from Control**		
				Difference	**95% CI for Difference**	**p-value***
Treatment	122	38	31.1%	8.0%	-3.1, 19.0	0.0797
Control	120	27	22.5%			
DAS28-CRP good/moderate EULAR response						
Group	**Total**	**Responder**	**%**	**Difference from Control**		
				Difference	**95% CI for Difference**	**p-value**
Treatment	122	74	60.7%	19.5%	7.3, 31.7	0.0048
Control	120	50	41.7%			
DAS28-CRP response (MCID -1.2)						
Group	**Total**	**Number**	**%**	**Difference from Control**		
				Difference	**95% CI for Difference**	**p-value**
Treatment	122	55	45.1%	13.2%	1.1, 25.3	0.0528
Control	120	39	32.5%			
HAQ-DI response (MCID -0.22)						
Group	**Total**	**Responder**	**%**	**Difference from Control**		
				Difference	**95% CI for Difference**	**p-value**
Treatment	122	56	45.9%	9.0%	-3.3, 21.4	0.0797
Control	120	44	36.7%			

*p-value based on the Cochran-Mantel-Haenszel test accounting for stratification.
Note: Baseline measured at time of consent; subject imputed as non-responder if rescued prior to Week 12, regardless of treatment assignment; subject imputed as non-responder if missing at Week 12.

Exploratory Endpoints

In the ITT population, 216 patients had RAMRIS scores measured at baseline and Week 12 (treatment 108, control 105). Prespecified subgroup analyses included patients with an erosive phenotype (treatment 53, control 45) and those that had failed only 1 prior b/tsDMARD (46 treatment, 36 control).

The proportion of bone erosion progressors by all patients and the subgroups of erosive phenotype and 1 prior b/tsDMARD are shown in **Table 21**.

Table 21: Proportion of Bone Erosion Progressors (> 0.05 Change in Erosion Score) from Baseline to Week 12 in All Patients and Erosive Phenotype

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	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

The mean score changes in bone erosion, synovitis and osteitis from baseline to Week 12 among all patients and the erosive phenotype and 1 prior b/tsDMARD subgroups are presented in **Table 22**.

Table 22: Mean Change in Erosion, Synovitis and Osteitis Scores at Week 12

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	0.0308
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

Discussion of Effectiveness Results through Week 12

Effectiveness was measured across multiple dimensions including ability to discriminate between response of treatment and control groups, achievement of Low Disease activity (LDA)

or remission, impact of treatment on progression of joint erosion, therapy persistence, and patient satisfaction.
ACR20 remains the outcome measure with the highest discriminating power between treatment and control groups at early time points and is often used as the primary endpoint in RA clinical studies.[2] ACR20 response at Week 12 showed a statistically significant difference between treatment (35%) and control (24%) groups (p-value = 0.0209, 95% CI 0.6 to 23.1). Patient-based assessments from ACR20 components include HAQ-DI, pain, and patient global assessment (PGA), for which each had outcomes that favored the treatment group.

While ACR20 has good discriminating power between treatment and control groups at early time points, it lacks sensitivity to change for describing treatment outcomes at the individual level and doesn't inform the patient's final disease activity level. Therefore, measures of disease activity, such as DAS28-CRP are considered for evaluating improvement in individual patients,[5] and support clinical decision-making for a Treat-to-Target approach, as outlined in RA treatment guidelines from the America College of Rheumatology.[1]

Evolution of Response in Open-Label Long-Term Follow-Up

The evolution of ACR20 response rate through Week 48 is presented in **Table 23**. Non-augmented represents patients on SetPoint System mono-therapy, i.e., without addition of b/tsDMARDs, increase in csDMARDs or high-dose steroid therapy.

Table 23: Evolution of ACR20 Response through Week 48

ACR20 Study Visit	Treatment (N=122) to TOL (N=121)			Control (N=120) to COL (N=120)			All (N=241)		
	n	% (n)	SE	n	% (n)	SE	n	% (n)	SE
Week 12	122	35.2% (43)*	0.04	120	24.2% (29)	0.04	--	--	--
Long-Term Follow-Up, All Completers									
Week 24	119	44.5% (53)	0.05	117	55.6% (65)	0.05	236	50.0% (118)	0.03
Week 36	119	47.9% (57)	0.05	115	55.7% (64)	0.05	234	51.7% (121)	0.03
Week 48	119	51.3% (61)	0.05	114	54.4% (62)	0.05	233	52.8% (123)	0.03
Long-Term Follow-Up, Non-Augmented									
Week 24	96	52.1% (50)	0.05	98	53.1% (52)	0.05	194	52.6% (102)	0.04
Week 36	89	51.7% (46)	0.05	87	62.1% (54)	0.05	176	56.8% (100)	0.04
Week 48	77	55.8% (43)	0.06	80	60.0% (48)	0.05	157	58.0% (91)	0.04

* p-value = 0.0209

Note: Baseline measured at time of consent; 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 subjects on SetPoint System monotherapy, i.e., without addition of b/tsDMARDs, increase in csDMARDs or high-dose steroid therapy.

SEs are presented on the probability scale.

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 24** and **Table 25**, respectively.

Table 24: Evolution of CDAI LDA or Remission Rates through Week 48

CDAI LDA/Remission Study Visit	Treatment (N=122) to TOL (N=121)			Control (N=120) to COL (N=120)			All (N=241)		
	n	% (n)	SE	n	% (n)	SE	n	% (n)	SE
Week 12	120	23.3% (28)*	0.04	119	16.0% (19)	0.03	--	--	--
Long-Term Follow-Up, All Completers									
Week 24	119	27.7% (33)	0.04	117	30.8% (36)	0.04	236	29.2% (69)	0.03
Week 36	117	33.3% (39)	0.04	114	35.1% (40)	0.04	231	34.2% (79)	0.03
Week 48	118	39.8% (47)	0.05	114	36.0% (41)	0.04	232	37.9% (88)	0.03
Long-Term Follow-Up, Non-Augmented									
Week 24	96	34.4% (33)	0.05	98	31.6% (31)	0.05	194	33.0% (64)	0.03
Week 36	87	39.1% (34)	0.05	87	40.2% (35)	0.05	174	39.7% (69)	0.04
Week 48	76	47.4% (36)	0.06	81	40.7% (33)	0.05	156	44.2% (69)	0.04

* p-value = 0.0648
Non-augmented represents subjects on SetPoint System monotherapy, i.e., without addition of b/tsDMARDs, increase in csDMARDs or high-dose steroid therapy.
SEs are presented on the probability scale.

Table 25: Evolution of DAS28-CRP LDA or Remission Rates through Week 48

DAS28 LDA/Remission Study Visit	Treatment (N=122) to TOL (N=121)			Control (N=120) to COL (N=120)			All (N=241)		
	n	% (n)	SE	n	% (n)	SE	n	% (n)	SE
Week 12	119	26.1% (31)*	0.04	119	15.1% (18)	0.03	--	--	--
Long-Term Follow-Up, All Completers									
Week 24	118	30.5% (36)	0.04	117	31.6% (37)	0.04	235	31.1% (73)	0.03
Week 36	114	33.3% (38)	0.04	107	37.4% (40)	0.05	221	35.3% (78)	0.03
Week 48	117	42.7% (50)	0.05	111	37.8% (42)	0.05	228	40.4% (92)	0.03
Long-Term Follow-Up, Non-Augmented									
Week 24	95	36.8% (35)	0.05	98	32.7% (32)	0.05	193	34.7% (67)	0.03
Week 36	85	36.5% (31)	0.05	82	42.7% (35)	0.05	167	39.5% (66)	0.04
Week 48	75	49.3% (37)	0.06	78	41.0% (32)	0.06	153	45.1% (69)	0.04

* p-value = 0.0154

Non-augmented represents patients on SetPoint System monotherapy, i.e., without addition of b/tsDMARDs, increase in csDMARDs or high-dose steroid therapy.

SEs are presented on the probability scale.

The evolution of proportion of patients that had an improvement in HAQ-DI score beyond the MCID from randomization through Week 48 is presented in **Table 26**. Non-augmented patients are those who are receiving stimulation therapy alone without addition of b/tsDMARDs or high-dose steroid therapy.

Table 26: Evolution of HAQ-DI Response (MCID) Rates through Week 48

HAQ-DI Response (MCID -0.22) Study Visit	Treatment (N=122) to TOL (N=121)			Control (N=120) to COL (N=120)			All (N=241)		
	n	% (n)	SE	n	% (n)	SE	n	% (n)	SE
Week 12	122	45.9% (56)*	0.05	120	36.7% (44)	0.04	--	--	--
Long-Term Follow-Up, All Completers									
Week 24	119	53.8% (64)	0.05	117	61.5% (72)	0.04	236	57.6% (136)	0.03
Week 36	118	57.6% (68)	0.05	115	58.3% (67)	0.05	233	57.9% (135)	0.03
Week 48	119	55.5% (66)	0.05	113	59.3% (67)	0.05	232	57.6% (133)	0.03
Long-Term Follow-Up, Non-Augmented									
Week 24	96	58.3% (56)	0.05	98	63.3% (62)	0.05	194	60.8% (118)	0.04
Week 36	89	59.6% (53)	0.05	87	58.6% (51)	0.05	176	59.1% (104)	0.04
Week 48	77	53.3% (41)	0.06	80	61.3% (49)	0.05	157	57.3% (90)	0.04

* p-value = 0.0787, adjusted for multiplicity using Hochberg Step-up Method

Note: Baseline measured at time of consent; subject imputed as non-responder if rescued prior to Week 12, regardless of treatment assignment; subject imputed as non-responder if missing at Week 12.

Non-augmented represents subjects on SetPoint System monotherapy, i.e., without addition of b/tsDMARDs, increase in csDMARDs or high-dose steroid therapy.

SEs are presented on the probability scale.

Therapy Persistence and Patient Satisfaction

Therapy persistence is defined as the continuation of therapy after it is initiated. It is an important measure of therapy tolerance and effectiveness for a condition like RA because it is a progressive and chronic disease. Without ongoing effective therapy, the risk for worsening of symptoms and disability increases. Real-world analysis from a large RA patient registry highlights that almost one-third of patients in the US discontinue initiated bDMARD therapies by 12 months and almost half by 24 months, most commonly due to loss of efficacy.[18] Additionally, primary patient non-adherence remains a challenge in RA, which has implications for delivery of clinical care.[17]

Continuation of treatment with the SetPoint System was assessed at Week 48 to evaluate therapy persistence. By Week 48, 97.5% of patients with an implanted device remained persistent with SetPoint Therapy and only about 25% of patients had augmented this therapy with a b/tsDMARD, despite there being no study restrictions for doing so (see **Table 27**). When viewed together with clinical outcomes at Week 12, the evolution of long-term clinical outcomes, and suppression of joint erosion, these results indicate a reasonable assurance of therapy effectiveness.

Table 27: Persistence with SetPoint Therapy (based on ITT)

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)
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)

Patient satisfaction with current RA therapies remains low as evidenced by the low therapy persistence rates with current therapies.[20] Consequently, there is a need for additional treatment options.

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 28**). Patient satisfaction was high, with 78% of study participants reporting they were somewhat to very satisfied and 94% reporting they would recommend the SetPoint System to a family member or friend.

Table 28: Patient Satisfaction / Recommend to Family or Friend

	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).

3. Subgroup Analyses

In prespecified subgroup analyses of patients with less than 4 vs 4 or more prior b/tsDMARDs, there was a trend towards greater efficacy observed in the subgroup with < 4 prior b/tsDMARDs (p for interaction= 0.0806). In the subgroup with 1 prior b/tsDMARD, ACR20 was achieved by 44.2% (23/52) receiving treatment vs. 19.0% (8/42) receiving control (p-value = 0.0054). Results for each subgroup of prior b/tsDMARDs are included in **Table 29**.

Table 29: ACR20 Response at Week 12 by prior b/tsDMARD subgroup (ITT)

Subgroup of 1 prior b/tsDMARD						
Group	**Total**	**ACR20 Responders**	**%**	**Difference from Control**		
				Difference	**95% CI for Difference**	**p-value**
Treatment	52	23	44.2%	25.2%	7.1. 43.3	0.0054
Control	42	8	19.0%			
Subgroup of 2 prior b/tsDMARDs						
Group	**Total**	**ACR20 Responders**	**%**	**Difference from Control**		
				Difference	**95% CI for Difference**	**p-value**
Treatment	25	8	32.0%	20.3%	-2.2, 42.9	0.0437
Control	28	3	10.7%			
Subgroup of 3 prior b/tsDMARDs						
Group	**Total**	**ACR20 Responders**	**%**	**Difference from Control**		
				Difference	**95% CI for Difference**	**p-value**
Treatment	15	3	20.0%	-17.6%	-51.1, 16.0	0.1643
Control	16	6	37.5%			
Subgroup of 1 prior b/tsDMARD						

Group	Total	ACR20 Responders	%	Difference from Control		
				Difference	95% CI for Difference	p-value
Treatment	30	9	30.0%	-2.4%	-24.1, 19.2	0.415
Control	34	12	35.3%			
Percentage calculated based on the ITT population. Differences in proportions and one-sided p-value (alpha: 0.025) based on the Cochran-Mantel-Haenszel test.						

4. Pediatric Exemption

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

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by clinical investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. RESET-RA included 90 investigators, between Principal Investigators (PIs) and Co-PIs (rheumatologist and surgeon). None of the clinical investigators had disclosable financial interests or arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Neurology Panel, an FDA advisory committee, for review and recommendation because the information in the PMA did not present any challenges to the review team in terms of interpretation. The review team determined that the results of the study were generally clear and therefore the review team determined that it would not be valuable to discuss these clinical topics or the nonclinical information before the Neurology Panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The RESET-RA pivotal clinical study was designed to evaluate the safety and effectiveness of the SetPoint System in adults with moderately-to-severely active RA who had an inadequate response, loss of response, or intolerance to 1 or more biologic or targeted-synthetic disease modifying antirheumatic drugs (DMARDs). This patient population is often referred to as a "bDMARD-IR population" (where IR stands for inadequate or intolerant response to a biologic) and represents a particularly challenging subset of patients for whom prior treatments have been unsuccessful. Effectiveness was measured across multiple dimensions including ability to discriminate between response of treatment and control groups, therapy persistence, and patient satisfaction.

The prospective multicenter randomized sham-controlled double-blind RESET-RA pivotal clinical study provided evidence to support a reasonable assurance of effectiveness of the SetPoint System. Blinding analysis indicated most patients and study personnel were unaware of group assignment.

Two-hundred-forty-two (242) patients were implanted with the Setpoint System and randomized to active stimulation (treatment, n = 122) or sham-control, non-active stimulation (control, n = 120). These patients comprise the intent-to-treat (ITT) population, and primary, secondary, and exploratory endpoints were conducted on the ITT population. The RESET-RA clinical study met its pre-specified primary effectiveness endpoint, demonstrating a statistically significant difference in the ACR20 response rate between active SetPoint treatment (35%) compared to the sham control (24%) groups (p-value = 0.0209, 95% CI 0.6 to 23.1).

The clinical benefits observed during the blinded study phase were durable, and continued to increase, in the long-term follow-up phase of the study. Treatment effects continued to improve through Week 24 and were stable and consistent through Week 48. In addition, marked improvements were observed after Week 12 on primary and secondary effectiveness outcomes in the sham control group following crossover and initiation of SetPoint therapy. Therapy persistence and patient satisfaction are high with SetPoint Therapy, which is a key determinant of effective treatment of RA.[13-17] At Week 48, 97.5% of patients remained persistent with SetPoint Therapy and only about 25% of patients had augmented this therapy with a b/tsDMARD, despite there being no study restrictions for doing so. Seventy-eight (78%) of study participants were somewhat to very satisfied after 12 weeks of active treatment; 94% would recommend the SetPoint System to a family member or friend.
The study population was reflective of the U.S. RA population. The prevalence of RA is 3 times higher in women than men, with incidence of RA in women being 4-5 times higher than that in men in people under 50 years of age.[12] The ITT population was predominately female (86%). Mean age was 55.7 years at time of consent. By race and ethnicity, most patients were White (80.6%), and representation by Hispanic or Latino was 18.6%.
When viewed in totality, the clinical outcomes at Week 12, the evolution of long-term clinical outcomes, high therapy persistence, low adjunctive b/tsDMARD utilization through 1-year follow-up and high patient satisfaction scores indicate there is a reasonable assurance SetPoint System is effective for its intended use.

B. Safety Conclusions

The risks of the device are based on non-clinical laboratory data as well as data collected in the RESET-RA clinical study. SAEs (serious adverse events) related to the device occurred in 1.6% of the 242 patients implanted and randomized, and all SADEs (serious adverse device effects) resolved. All events were related to the implantation procedure, no SADE occurred after Week 12, and no SADE could be attributed to SetPoint stimulation or the SetPoint device. No deaths attributed to the device (or otherwise) occurred in the study and there were no unanticipated adverse device effects (UADE).

The total number of SAEs in the blinded phase through Week 12 was low (12 events in 9 patients) and equally distributed in both study groups (5 events in 4 treatment patients vs. 7 events in 5 control patients). However, a number of device deficiencies and device-related protocol deviations were reported in the pivotal study that could have affected subject safety had they not been identified in this clinical trial environment. These mainly involved the charging/programming Charger component being unable to connect to the implant, and the surgeon cauterizing in the presence of the implant, requiring device replacement due to potential damage.

These device issues were resolved by re-designing the Charger to address manufacturing issues observed in the clinical study, and revising the labeling to include a minimum allowable distance (2 cm) between electrocautery and the Implant. However, the final device design was not evaluated in subjects enrolled in the pivotal study or another study. As a result, SetPoint Medical is required to provide real-world data via a Post-Approval Study. As specified in the Conditions of Approval Agreement, the Post-Approval Study is intended to demonstrate the device design changes and revised labeling, collectively, further support a reasonable assurance the SetPoint System is safe when used as intended.

Notwithstanding the device performance and procedural issues discussed above, the overall adverse effect profile is favorable.

C. Benefit Risk Determination

The probable benefits of the SetPoint System are based on the results of the RESET-RA clinical study. Effectiveness was demonstrated by clinical outcomes at Week 12, the evolution of long-term clinical outcomes, high therapy persistence, low adjunctive b/tsDMARD utilization and high patient satisfaction scores. The totality of effectiveness outcome data provides a reasonable assurance of the effectiveness of the SetPoint System.

For safety, the risk assessment concluded the implantation and explantation procedures and the stimulation therapy were well-tolerated. If necessary, the device could be safely explanted without damaging the vagus nerve. The rate of serious adverse events related to the implantation procedure was low, with all events successfully managed to resolution. No malignancies, major cardiac events, or serious infections were associated with SetPoint Therapy. During long-term follow-up, no safety concerns have been identified, and no device revisions have been required. The totality of the safety data provides a reasonable assurance of safety.

In weighing the clinical benefit demonstrated by the SetPoint System and the risks associated with the SetPoint System, the probable benefit outweighs the probable risks.

D. Patient Perspectives

Patient satisfaction results showed that 78% of study participants reported they were somewhat to very satisfied after 12 weeks of active treatment, and 94% would recommend the SetPoint System to a family member or friend.

E. Overall Conclusions

Given the available information cited above, the data support that, for treatment of moderate-to-severe RA, the probable benefits of the SetPoint System outweigh the probable risks.

XIV. CDRH DECISION

CDRH issued an approval order on July 30, 2025. The final clinical conditions of approval cited in the approval order are described below.

Conditions of Approval

- SetPoint Medical (SPM) will provide information to FDA regarding the training and training materials for the SetPoint System as follows:
    - The training and training material provided to:
        - The on-site SetPoint Medical representatives that will be present for each surgeon's first five (5) implantation procedures;
        - Surgeons and supporting surgical/operative staff;
        - Patients and prescribers regarding charging procedures and identifying when the device is functioning properly;
    - If any involved person is trained without any written materials, a description of the manner in which this training will occur in a real-world context.
    - Documentation of training that includes the date, purpose, method(s), and the name, professional experience and qualifications of SPM representatives and surgical attendees, and performance (e.g., Pass/Fail, Complete/Incomplete) of surgical attendees.
- SetPoint Medical will conduct a SetPoint System Safety and Performance Post-Approval Study to monitor safety and technological performance to further support the safety and effectiveness of device design changes made after completion of the pivotal study and to validate adequate real-world use of the final, finished device outside of the controlled environment of a clinical study. Specifically, this study will involve the following:
    - Creation of a registry of patients implanted with the SetPoint System, the prescribing physician and the implant/explant surgeon to enable systemic tracking and analysis of this real-world data (RWD)
    - The registry should be set up to collect the following patient, physician, surgeon, and device information and data:
        - Patient age and sex
        - Other appropriate demographic information such as duration of patient's rheumatoid arthritis (RA) diagnosis and history of patient's past RA treatment
        - Rheumatologist identifier and experience
        - Surgeon identifier and general vagus nerve surgery experience level
        - Identification of SetPoint implant procedure training and number of prior SetPoint implant procedures completed
        - Implantation site and date
        - SetPoint representative assigned to procedure (if applicable)
        - Device serial number and lot number
        - Whether cauterization needed to be used, or other intraoperative complications/deviations from standard procedure
        - Whether the device required replacement and the reason (e.g., cauterization needed to be used)
        - Device performance monitoring
            - Battery status and chargeability at time of implant activation and onwards

        - Connectivity problems
        - Programming difficulties
        - Periods of non-functionality or unplanned treatment interruption
        - Patient-reported complaints regarding charging or device function
      - Patient clinical outcomes relative to device performance monitoring collected every 6 months for a 3-year reporting period
  - Enrolling an adequate number of patients to: 1) track adverse events (AEs) and device deficiencies associated with procedure deviations; 2) provide an adequate sample size to demonstrate mitigation of device failures; and 3) track adverse events associated with device failures. The registry should include an adequate number of experienced surgeons who have completed at least 5 unsupervised SetPoint System implantation procedures;
  - Monitoring deviations in clinical procedures and device use, including but not limited to, procedural mistakes, patient misunderstanding, and unplanned extended periods without treatment delivery;
  - Tracking instances where cauterization within 2cm of the implant is required and implementation of proactive implant replacement protocols;
  - Submitting reports within 10 working days of SetPoint becoming aware of instances requiring device replacement due to cauterization within 2 cm of the device, or a device deficiency requiring intraoperative replacement or post-operative explantation; and
  - Collecting data continuously from all ongoing SetPoint System implantation procedures in the registry and submitting reports every six months during and after enrollment, for up to 3 years.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820), which was in effect at the time of the inspection. As of February 2, 2026, the revised part 820, referred to as the Quality Management System Regulation (QMSR), is effective.

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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