CLINICAL INVESTIGATIONAL PROTOCOL

1 TITLE PAGE

Study Title	Vagus Nerve Stimulation Using the SetPoint System for Moderate to Severe Rheumatoid Arthritis: The RESET-RA Study
Protocol Number	SPM-020
ClinicalTrials.gov ID	NCT04539964
Investigational Device	The SetPoint System
Indication for Use / Breakthrough Device Designation (Q240179)	The SetPoint system is indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response, loss of response or intolerance to one (1) or more biological or targeted synthetic DMARDs
Study Design	An operationally seamless, 2-stage, randomized, sham-controlled, double-blind, multicenter, pivotal study with a 12-week follow-up for the primary efficacy endpoint, followed by one-way crossover of the control group and a 252-week open-label follow-up of all subjects on active stimulation for long-term safety
Study Sponsor's Name and Address	SetPoint Medical, Inc. 25101 Rye Canyon Loop Valencia, CA 91355 U.S.A.
National Co-Principal Investigators	Rheumatology: John Tesser, MD Arizona Arthritis and Rheumatology Research, P.C. 9520 W. Palm Lane, Suite 220 Phoenix AZ, 85037 Surgery: Mark Richardson, MD PhD Director, Functional Neurosurgery Massachusetts General Hospital 55 Fruit Street Boston, MA 02114 U.S.A.
Data Management and Monitoring	SetPoint Medical, Inc.
Biostatistics and Data Analysis	SetPoint Medical, Inc.

This study will be conducted under the guidance of the International Council on Harmonisation (ICH) Good Clinical Practice (GCP), Clinical investigation of medical devices for human subjects – GCP (BS EN ISO 14155), and other applicable local and federal regulations, including the archiving of essential documents.

The study-related COVID-19 contingency measures to assure the safety of study subjects, maintain compliance with GCP, and minimize risks to study integrity for the duration of the COVID-19 pandemic are detailed in Section **19.**

Revision History

Revision	Revision Date	Summary of Changes
A	13MAR2020	Acquisition of document number
B	21MAY2020	Initial release
C	08OCT2020	• Moved baseline assessments for the primary and key secondary efficacy endpoints from Day 0 to the day of consent, as recommended by the FDA. • Moved baseline assessments, including MRI, for the exploratory endpoints from Day 0 to Screening, as recommended by the FDA. • Expanded prior b/tsDMARD from 1-3 to 1 or more (p. 35) • Removed Confirmation of RA Severity visit • Shortened window between Implant Procedure and Day 0 visit • Opened Titration 1-3 visit windows • Added pregnancy test to Titration 1-3 • Added blood collection for CBC • Changed Principal Investigator to Co-Principal Investigator Rheumatologist and Sub-Investigator to Co-Primary Investigator Surgeon • Adjusted sample size from 70 to 60 in Stage 1 and from 180 to 190 in Stage 2 (p. 15, 34) • Reduced the maximum number of subjects per site from 40 to 20 (p. 34) • Added subject washout status to Screening (p. 40) • Removed Early Termination Visit • Updated statistical section with power calculations for 250 subjects and a broader range of sham effect (p. 61) • Updated definitions of analysis populations (p. 63) • Defined major procedural protocol deviations (p. 64) • Added authorship requirements (p. 73) • Added COVID-19 contingency measures (p. 73)
D	17NOV2020	• Added definitions of EGA, SGA and subject's pain assessment under Definitions and removed them from text (pp. 12, 15) • Added CBC to Screening in Schedule of Assessments (p. 21) • Added ACR20 at Week 12 from Day 0 to key secondary endpoints (p. 35) • Moved HAQ-DI score change from baseline to Week 12 from key secondary to exploratory endpoints (p. 35) • Modified exclusion #3 for corticosteroid injections from within 28 to 30 days of Implant Procedure (p. 37) • Modified exclusions #4 and #5 to change timepoint by when concomitant use of glucocorticoids and NSAIDs must be stable from Implant Procedure to informed consent (p. 37)

Revision	Revision Date	Summary of Changes
		• Modified exclusion #6 to restrict subjects not agreeing to abstain from nicotine products throughout study (p. 38) • Updated exclusion #17 to include pre-surgical X-ray (p. 38) • Updated exclusion #35 to specify investigational drug for RA (p. 39) • Added exclusion # 40 for subjects that work or reside in areas with high RF (p. 39) • Clarified options for explant or decommissioning upon withdrawal (p. 41) • Included collection of vital signs, height, and weight to Screening and baseline assessments (p. 42) • Added final evaluation of eligibility to end of Screening and baseline assessments (p. 43) • Listed X-ray views required for pre-surgical clearance (p. 43) • Clarified that pregnancy test is done, as required, at titration visits (p. 46) • Added unblinding after completion of Week 12 to inform decision about participation in the long-term extension study (pp. 47, 71) • Added figure showing study visit timeline (p. 49) • Removed female sterilization as a method of birth control (p. 49) • Updated required period of stability for allowed medications (p. 53) • Updated reporting schedule to sponsor for device-related AEs from 10 working days to 24-48 hours (p. 56) • Added scarring to risks associated with surgical implantation (p. 59) • Added risk of concomitant csDMARDs and VNS therapy (p. 59) • Updated training requirements (p. 66) • Clarified role of unblinded technicians (p. 70) • Updated COVID-19 Contingency Measures to allow only Week 4 or Week 8, not both, to be conducted remotely, allow virtual re-consent and include CBC to blood collection under Study Procedures During COVID-19 (p. 77)
E	05MAY2021	• Updated study title (pp. 1, 21) • Changed “moderate-to-severe” to “moderate to severe” throughout document • Added ClinicalTrials.gov identifier (p. 1) • Updated description of study design to include one-way crossover and open-label, long-term follow-up (pp. 1, 21-22, 44, 56) • Added abbreviations bDMARD, csDMARD, MMP3, PMA, SAA, and tsDMARD and removed PCB (pp. 12-14) • Added definitions for crossover, crossover PTE population, open-label PTE population and rescue treatment; separated definition of EULAR response criteria from DAS28-CRP; updated definition of PTE population (pp.15-18)

Revision	Revision Date	Summary of Changes
		• Added that blinding will be maintained until all subjects have completed Week 12 assessments and database is locked (pp. 21, 43, 83-84) • Clarified that pause between Stage 1 and Stage 2 pertains to a pause in enrollment (pp. 21, 43, 59) • Added statement that initial 12-week follow-up data will support PMA application and additional follow-up will evaluate long-term safety (pp. 21, 43) • Removed term "therapeutic" from description of active stimulation and replaced "non-therapeutic" with "non-active" to describe sham stimulation (pp. 21, 44, 53) • Removed reference to offering participation in a separate, long-term, open-label extension study in which all subjects receive active stimulation. (pp. 21, 56) • Added that control group will crossover to active stimulation after completion of Week 12 assessments (pp. 1, 21-22, 43, 44) • Under study population, updated note to state that 10% reflects JAKi usage in the "target" RA population, instead of "general" (pp. 22, 45) • Added allowance to miss up to 2 doses of csDMARD due to COVID-19 vaccination, except in the 4 weeks prior to informed consent (pp. 22, 45, 63) • Removed reference to equivalent dose of methotrexate for required background RA therapy (pp. 22, 45) • For allowed concomitant medications, clarified that mild oral opiates taken on a regular basis may be continued and those taken only as needed are allowed except 24 hours prior to assessments (pp. 23, 64) • Removed reference to subject being eligible for rescue therapy in a separate, extension study if they do not achieve ACR20 improvement (pp. 23, 57) • Added that rescue treatment is allowed after subject completes Week 12 assessments and that the need, timing, and type of rescue treatment are at the discretion of the Co-PI Rheumatologist and the subject (pp.23, 44, 65-66) • For allowed concomitant medications, clarified that dose must remain stable through completion of Week 12 assessments and subjects not taking these at the time of informed consent should not start until completion of Week 12 assessments (pp. 23, 64) • Extended duration of study participation by adding 18 visits as part of open-label, long-term follow-up after completion of Week 12 (pp. 23, 56) • Added resuming stimulation and implant decommissioning as reasons for an unscheduled visit (pp. 23, 57) • Added Co-Primary Rheumatologist's blinding assessment at Week 4 and 12 (pp. 23, 25, 27, 55, 84, 92) • Extended duration of study participation by 3.5 years to reflect

Revision	Revision Date	Summary of Changes
		addition of long-term follow-up (pp. 24, 59) • Updated study flow diagram to add crossover of the control group after Week 12 assessments, open-label, long-term follow-up, requirements on application of rescue treatment, and optional explant procedure; clarify allowed concomitant medications; and to include changes to schedule of assessments noted below (pp. 25-26) • Updated schedule of assessment to remove reference to Week 12 as EOS; added vital signs to Screening, Day 0 and Week 12; added SF-36 and EQ-5D-5L to Day 0; added 12-lead ECG to Week 12; add blinding assessment for Co-PI rheumatologist; and added dose titration to Week 12 (pp. 27, 55, 56) • Added schedule for assessments for open-label, long-term follow-up (pp. 28, 56) • Updated Figure 1 reference to study device from "NCAP" to "SetPoint System" and correct typo (p. 31) • Indicated range of output currents (p. 33) • Added description of Energizer Wireless Charger (p. 33) • Editorial changes to description of SPM-008 (pp. 39) • Updated status of SPM-011 to current (p. 41) • Added exploratory endpoints for open-label, long term follow-up (pp. 42-43) • Updated examples of biomarkers to be analyzed (p. 43, 61) • Updated period of reporting for incidence of AEs and device deficiencies to include open-label, long-term follow-up (pp. 43, 78) • Added types and dosages for csDMARDs permitted as RA background therapy and included allowance for lower doses in the case of dose limiting toxicity (pp. 45, 63) • Modified exclusion #10 by adding an exception for infections cleared before Implant Procedure (pp. 46, 50) • Added statement that in the event subject becomes or wants to become pregnant, implant will be decommissioned, and subject followed for safety (pp. 46, 59) • Corrected definition for subject status of "screen failure" and updated definition of "completed study" to include period of open-label, long-term follow-up (p. 48) • Added information on the possible need for re-consent (p. 50) • Added a heading for information on device check and dose titration/adjustment (p. 54) • Added information on monitoring implant charge level and possible decommissioning in the event 0% charge level is observed (pp. 54, 57-58) • Added requirement for subjects that have their implant decommissioned to continue adhering to study visits and procedures. Subjects that choose to end participation after decommissioning are asked to contact the investigator in the event of a safety issue (p. 58)

Revision	Revision Date	Summary of Changes
		• Added requirement to record the need, type and timing of rescue treatment to follow-up visits after Week 12 (p. 56) • Added instruction for Co-PI Rheumatologist to discuss subject options during open-label long-term follow-up and to document decision made (pp. 55-56) • Added information on re-registering MicroRegulator and crossover of control group to active stimulation following week 12 assessments (p. 56) • Changed referenced to "Clinician Standby Mode" to "Suspending Therapy" (p. 56, 58) • Added requirement to decommission implant at end of study (p. 56) • Added section describing suspending and resuming stimulation including information on when stimulation must and can be suspended, how to perform suspension and study treatment during period of suspension (p. 57) • Removed list of visits and visit windows in section 11.6 since redundant with schedule of assessments (pp. 55-56) • Added information on risk of using csDMARD during pregnancy (p. 59) • Expanded type and corrected categorization of contraception methods (p. 60) • Added that clinical laboratory samples will be analyzed centrally through Week 24 and locally from Week 36 through Week 192 (p. 61) • Added allowance for dose adjustments to background therapy for the management of toxicity and requirement to record toxicity as an adverse event (pp. 63) • Added allowance for perioperative changes to background RA therapy and allowed concomitant medications at discretion of investigator to manage risks associated with implant procedure (pp. 63, 64) • Added that risks associated with use of csDMARDs should be discussed with subject (p. 63) • Added that restriction on concomitant use of steroid pulse therapy, b/tsDMARDs, and steroid injections applies only through completion of Week 12 assessments (p. 64) • Added possible need to suspend stimulation, decommission implant or surgically remove implant in the event subject requires a prohibited medical intervention (p. 65) • Added that results from RA disease activity assessments collected at follow-up visit can be used for decision making on rescue (p. 65) • Added that subjects that are rescued may continue their assigned study treatment and that rescued subjects should continue to follow the study visit schedule, adhere to all study procedures and be monitored for safety (p. 66) • Added "indeterminate" as a relationship classification for AEs (pp. 66, 67)

Revision	Revision Date	Summary of Changes
		• Added section on AE expectedness (p. 67) • Added section on AE adjudication (pp. 67-68) • Removed format for reporting of a death, SAE, and device-related AE (p. 69) • Added potential risks: eructation, constipation, vomiting or gagging, seroma, weight change and neutropenia (pp. 71-72) • Included rescue treatment with potential risks related to concomitant use of VNS with csDMARDs (p. 72) • Added analysis of exploratory endpoints to gather additional efficacy and long-term safety data (pp. 42-43, 78) • Clarified how decisions on rescue are made, types of medications are considered as rescue, how data are handled (pp. 65-66) • Added that subjects initiating rescue treatment during open-label long-term follow-up are treated as non-responders (p. 66, 78) • Added definitions for open-label and crossover PTE populations (p. 79) • DMC meeting schedule updated to specify frequency during Stage 1 enrollment, Stage 2 enrollment and open-label, long-term follow-up (p. 82) • Removed allowance for investigator to directly obtain treatment assignment and added process for requesting unblinding in exceptional circumstances in which knowledge of treatment assignment is necessary to manage the subject (pp. 83-84) • Clarified blinding and unblinding rules (pp. 83-84) • Removed revealing treatment assignment to subject and Co-PI Rheumatologist upon completion of Week 12 assessments (p. 84) • Added responsibility of Co-PIs to ensure timely delivery of source documentation required for adjudication and reporting of AEs (p. 85) • Added information on COVID vaccination with concomitant immunomodulatory therapies (p. 92) • Made minor clarifications, edits and editorial changes throughout
F	19OCT2021	• Identified study as breakthrough device (p. 1) • Increased number of Stage 1 sites to 25 (pp. 22, 44) • Clarified prior JAKi use conditions upon which stratification and population limits are based (pp. 22. 47, 77, 78) • Clarified background csDMARD requirements (p. 46, 64) • Clarified that exclusion for significant cardiovascular disease applies to current, clinically significant conditions (p. 47) • Corrected description of inclusion criterion on kidney function and adding requirement that eligibility be confirmed prior to screening MRI (p. 48, 52, 74) • Added uncontrolled sleep apnea as an example of a pulmonary disease that would render a patient ineligible for participation (p.

Revision	Revision Date	Summary of Changes
		48) • Correct exclusion #41 to replace reference to a 12-week study with more specific information about 6-7 week screening and post-surgical clearance and 192 weeks of follow up (p. 49) • Require that the Co-PI Surgeon perform Pre-surgical Clearance, as opposed to a designee (p. 53) • Added detail describing pre-surgical clearance (p. 53) • Require that the Co-PI Surgeon or designee at the surgical site, as opposed to the rheumatology site, perform Post-surgical Clearance (p. 54) • Clarified meaning of childbearing potential and conditions under which a pregnancy test is not necessary (p. 60) • Require that the same joint evaluator conduct the Tender and Swollen Joint Counts and Evaluator Global Assessment at Screening and Week 12 (p. 62) • Removed DMC's role in making treatment recommendations in order to preserve study blind. In the event Co-PI Rheumatologist believes knowledge of treatment assignment is essential for management of a subject, they must request and receive authorization from Sponsor CMO. The decision and rationale to unblind will be documented and presented for review by the DMC to ensure concurrence with the recommendation. If unblinding is recommended and the DMC concurs, the CMO with authorize the Co-PI Rheumatologists access to the treatment assignment in IRT (p. 85)
G	10FEB2022	• Removed 10% study population limit on subjects with JAKi intolerance (limit on JAKi failure or loss of response is maintained) (pp. 22, 23, 46, 47, 77, 78) • Added statement that in the case of full discharge, the MicroRegulator battery cannot be recharged and must be decommissioned. Once decommissioned, the subject must return their Energizer and Wireless Charger (pp. 55, 59) • Added requirement for Co-PI Rheumatologist to review risks, particularly black box risks, that are associated with any rescue treatment prescribed. Also, to discuss any additional tests or monitoring required to mitigate such risks (pp. 67, 74) • Added Appendix B: FDA Drug Safety Communication (DSC) issued on 09/01/2021 about JAK inhibitor (pp. 101-107)
H	10MAR2022	• Added the risk of aspiration as a result of swallowing difficulty (pp. 73, 74)
I	29SEP2022	• Add 5 U.S. study centers, for a total of 45 sites (pp. 23, 45) • Add stratification for subjects with inadequate response or loss of response to ≥4 biological DMARDs (bDMARDs) with ≥ 2 mechanisms of action (pp. 23, 79) • Limit the total number of subjects who have experienced JAKi failure or loss of response from 10% of the study population (i.e., 25 subjects) to a total of 6 subjects (already enrolled in Stage 1) (pp. 24, 47, 48, 80)

Revision	Revision Date	Summary of Changes
		• Provide additional guidance on the exclusion of subjects with cervical spine disorder or instability to include subjects that, in the opinion of the investigator, could be exacerbated by the investigational implant procedure (p. 49) • Provide additional guidance on medical conditions that could put subject at increased risk for surgical complications (pp. 49-50) • Extend use of central laboratory for entire duration of study (p. 64) • Add Energizer to the list of options for assessment of AE relationship (p. 69) • Removed detail not relevant to power calculation from footnote of Table 4 (p. 80) • Clarify how interim analysis data is submitted to FDA (to reflect what was done for Stage 1 report submission) (p. 81) • Add exploratory analysis of subjects combining rescue therapy with VNS (p. 82)
J	07NOV2022	• Added indication to Title Page (p. 1) • Clarified 5th bullet under Revision History, Summary of Changes (p. 9) • Updated MicroRegulator charge level threshold for counseling subject on importance of regular charging from 85% to 75% to align with modifications made to Energizer LED and audible indicators for MicroRegulator state of charge which was approved per FDA submission G170231/S026 (pp. 56, 60) • Added "to reduce the risk of potential…post-operative pain" as an allowed reason for making temporary, perioperative changes to allowed concomitant medications (p. 67)
K	15MAY2023	• Removed indication for Breakthrough Device Designation from title page (p. 1) • Replaced National Co-PI Rheumatologist (from Dr. Curtis to Dr. Tesser) (p. 1) • Clarified total number of study centers in Stage 1 and 2 as a limit, not an actual (pp. 23, 45) • Updated exclusion criterion #6 to exclude regular use of and dependency on nicotine product within the past two years. Previously exclusion was for current use (p. 48) • Added additional examples of outcome measures that could be confounded by fibromyalgia to exclusion criterion #15 (p. 48) • Added exclusion of patients with BMI at screening of ≥ 35kg/m^2 (p. 50) • Added exclusion for use of high potency opioids (p. 50) • Added exclusion of patients with inflammatory joint disease other than RA (p. 50) • Added examples of mild oral opiates that are allowed (p. 67) • Updated frequency of DMC meetings to be consistent with charter (p. 86)

Revision	Revision Date	Summary of Changes
L	29JAN2024	• Updated enrollment from "up to 250 randomized subjects" to "at least 240 and up to 250 randomized subjects" and included information for 240 subjects in power analysis (pp. 24, 46, 82 and 83) • Introduced and defined new term "augmented therapy" to describe the addition of treatment for RA therapy after completion of Week 12 assessments (pp. 18, 70, 71, 84) • Updated units for hsCRP to reflect how central lab reporting results (p. 21) • Added details on the specific types of treatments that are considered "rescue," along with the data imputation rule specified for subjects receiving rescue (pp. 22, 70) • Added Energizer as a relationship classification for consistency with categories specified in section 15.1, Specification of Safety Parameters (p. 71) • Added detail on adjudication of stimulation-related adverse events once the study is unblinded. If subject has AE classified as stimulation-related but was assigned to the control group, classification will be updated to "not related" (p. 72) • Updated to reflect communication procedures that took place for the Interim analysis, consistent with G170231/S028 (p. 83) • Renamed "Open label PTE population" to "Treatment to Open Label (TOL) population" and "Crossover PTE population" to "Control to Open Label (COL)" for clarity and for consistency with SAP (pp.19, 23, 84) • Removed "If a subject decides to discontinue from the study, every attempt will be made to continue to collect the safety data according to the protocol procedures" from definition of safety population since no allowed mechanism exists for collecting safety data after a subject withdraws from the study (p. 84) • Described locking of the primary dataset (versus entire dataset) when referencing the point at which the study will be unblinded (pp. 24, 46, 70, 89)
M	16JUL2024	• Extended duration of study participation by adding 6 visits as part of open-label, long-term follow-up after completion of Week 12 (pp. 25, 26, 27, 28, 47, 59, 61, 64) • Updated Sections 5.2 and 6.2 Long-Term Follow-up to include visits from Week 204 through Week 264 (EOS) (pp. 30, 32) • Updated the evaluation period of incidence of AEs, SAEs, and device malfunctions through Week 264 (EOS) (p. 47, 72, 85) • Updated Figure 12: SPM-020 Study Schematic to extend Open-label, Long-term follow-up to 252 weeks with end of study at Week 264 (p. 48) • Updated Figure 13: SPM-020 Study Timeline to extend Open-label, Long-term follow-up to 252 weeks with end of study at Week 264 (p. 64) • Added that blood samples from Week 204 through Week 264 (EOS) will be analyzed locally (p. 66)

Revision	Revision Date	Summary of Changes
		• Updated procedure for distribution of Unblinding information (p. 90)

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2 LIST OF ABBREVIATIONS

Abbreviation	Expansion
ACh	Acetylcholine
ACPA	Anti-citrullinated peptide antibody
ACR	American College of Rheumatology
AE	Adverse event
α7nAChR	Alpha 7 nicotinic acetylcholine receptor
bDMARD	Biologic DMARD
BS EN	British Standard European Norm
CAP	Cholinergic anti-inflammatory pathway
CARLOS	Cartilage loss score
CBC	Complete blood count
CDAI	Clinical Disease Activity Index
ChAT+	Choline acetyltransferase
CIA	Collagen-induced arthritis
Co-PI	Co-principal investigator
CRF	Case report form
CRP	C-reactive protein
csDMARD	Conventional synthetic DMARD
CTA	Clinical trial agreement
DAS	Disease Activity Score
DMARD	Disease-modifying anti-rheumatic drug
DMC	Data monitoring committee
ECG	Electrocardiogram
EDC	Electronic data capture
EGA	Evaluator's global assessment
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EMR	Electronic medical records
EQ-5D-5L	EuroQol 5 domains 5 levels
EULAR	European League Against Rheumatism

Abbreviation	Expansion
GBCA	Gadolinium-based contrast agents
GCP	Good clinical practice
HAQ-DI	Health Assessment Questionnaire Disability Index
hsCRP	High-sensitivity C-reactive protein
ICF	Informed consent form
IFU	Instructions for use
IL	Interleukin
IRB	Institutional review board
IRT	Interactive response technology
ISO	International Organization for Standardization
ITT	Intent to treat
JAKi	Janus kinase inhibitor
LDA	Low disease activity
LED	Light emitting diode
LPS	Lipopolysaccharide
MCID	Minimal clinically important difference
MCS	Mental component summary
MMP3	Matrix metalloproteinase-3
MRI	Magnetic resonance imaging
NCAP	Neurostimulation of the cholinergic anti-inflammatory pathway
NRS	Numerical rating scale
NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
PCS	Physical component summary
PMA	Premarket Approval
POD	Positioning and Orientation Device
PTE	Per-treatment evaluable
QD	Every day
QID	4 times a day
RA	Rheumatoid arthritis
RAMRIS	Rheumatoid Arthritis MRI Scoring System

Abbreviation	Expansion
RCT	Randomized controlled trial
RF	Rheumatoid factor
SAA	Serum amyloid A
SADE	Serious adverse device effect
SAE	Serious adverse event
SC	Subcutaneous
SF-36	Short Form Survey with 36 items
SGA	Subject's global assessment
SJC28	Swollen joint count in 28 joints
Sub-I	Sub-investigator
TEAE	Treatment emergent adverse event
TENS	Transcutaneous electrical nerve stimulation
TJC28	Tender joint count in 28 joints
TNF	Tumor necrosis factor
tsDMARD	Targeted synthetic DMARD
UADE	Unanticipated adverse device effect
UAT	User acceptance testing
UI	User interface
USADE	Unanticipated serious adverse device effect
VNS	Vagus nerve stimulation

3 DEFINITIONS OF TERMS

Term	Definition
ACR20/50/70	A composite measure defined as improvement of 20, 50 or 70% in: • TJC28 • SJC28 And 3 out of the following 5 criteria: • Subject's pain assessment • SGA • HAQ-DI • EGA • hsCRP (mg/mL)
Adverse device effect	AE related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. [BS EN ISO 14155]
AE	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. [BS EN ISO 14155]
Augmented therapy	Additional treatment for RA therapy applied *after* completion of Week 12 assessments, during open-label, long-term follow-up. Augmented therapy may be applied at any time during long-term follow-up. The decision about the need, type and timing of treatment is left to the discretion of the Co-PI Rheumatologist and the subject. Subjects combining stimulation with the following additions to RA therapy will fall into the augmented therapy subgroup for analysis of response rates for key efficacy endpoints at specific timepoints: • *Prednisone equivalent >10 mg/day*. If average daily corticosteroid use exceeds 10 mg/day prednisone after a period (time from previous visit up to the day before the current visit), the subject is assigned to the augmented therapy subgroup for that visit. • *Corticosteroid injection*. If subject received a corticosteroid injection within 30 days prior to a study visit, the subject is assigned to the augmented therapy subgroup for that visit. • *b/ts/csDMARD*. Subjects who receive treatment with biologic, targeted synthetic, or additional conventional synthetic DMARD, or increased dose of background conventional synthetic DMARD will be assigned to the augmented therapy subgroup for all subsequent visits.
Baseline	Information and values collected during Screening. The RA disease activity assessments that serve as the baseline assessments used for determination of the primary and key secondary efficacy endpoints must be performed on the day of informed consent.
CDAI	The CDAI score is based on 4 items: • TJC28 • SJC28

Term	Definition
	• 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 The MCID is a score reduction by 12 if starting in high activity, 6 if starting in moderate activity, and 1 if starting in low activity.
Control to Open Label (COL) population	Control subjects from ITT population who received non-active (sham) stimulation through Week 12, 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.
Crossover	The process of switching from an initially assigned treatment to the other treatment being studied.
DAS28-CRP	The DAS28-CRP score is a composite index providing a measure of disease activity, comprising: • TJC28 • SJC28 • SGA • hsCRP (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 The DAS28-CRP score corresponds to the current RA activity: • 0 to < 2.6 Remission • 2.6 to < 3.2 LDA • 3.2 to ≤ 5.1 Moderate activity • > 5.1 High activity A DAS28-CRP score reduction by 1.2 represents the MCID.
Day 0 (randomization, initiation of stimulation)	Scheduled study visit occurring 14 to 21 days after Implant Procedure during which subjects undergo the following study procedures in the order specified: • Day 0 assessments • Randomization • Initiation of stimulation Subjects must receive final surgical clearance with an approval to initiate study treatment before proceeding to the Day 0 visit.
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling. [BS EN ISO 14155]

Term	Definition
Device malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation protocol. [BS EN ISO 14155]
DMC	An independent data monitoring committee responsible for safeguarding the interests of study participants, assessing the safety and efficacy of the interventions during the study, and for monitoring the overall conduct of the clinical study.
EGA	A global assessment of the subject's RA activity performed by an independent, blinded Joint Evaluator using NRS from 0 (inactive) to 10 (very active).
EQ-5D-5L	A standardized instrument for measuring general health status within the following 5 dimensions: • Mobility • Self-care • Usual activities • Pain/discomfort • Anxiety/depression Each dimension is scored on 5-point scale as: • No problems • Slight problems • Moderate problems • Severe problems • Extreme problems In addition, general health status is scored from 0 (the worst health) to 100 (the best health).
Enrolled	Subjects meeting all the inclusion and none of the exclusion criteria in whom the implant procedure is attempted.
EULAR response criteria	A means of measuring efficacy of treatment using DAS28-CRP, incorporating both an absolute measure of disease activity, and a measure of change in activity. A subject is considered having a moderate treatment response if: • DAS28-CRP score improvement from baseline to Week 12 is > 0.6 and ≤ 1.2, and the DAS28-CRP score at Week 12 is ≤ 5.1; or • DAS28-CRP score improvement from baseline to Week 12 is > 1.2, and the DAS28-CRP score at Week 12 is > 3.2. A subject is considered having a good treatment response if: • DAS28-CRP score improvement from baseline to Week 12 is > 1.2 and the DAS28-CRP score at Week 12 is ≤ 3.2
Flare	Worsening of RA symptoms resulting in an increase between consecutive visits in DAS28 score ≥ 1.2, or an increase ≥ 0.6 if the first of the paired visits had DAS28 ≤ 3.2.
HAQ-DI	A questionnaire validated for RA self-assessment by subjects that contains 20 questions in the following 8 functional areas: • Dressing and grooming • Arising

Term	Definition
	• Eating • Walking • Hygiene • Reach • Grip • Common daily activities Scoring within each functional area is from 0 (without any difficulty) to 3 (unable to do). The total score is obtained by summing 8 area scores and dividing by 8. The total HAQ-DI score ranges from 0 to 3 and corresponds to the current degree of disability: • 0 to < 1 Mild difficulties to moderate disability • 1 to < 2 Moderate disability • 2 to 3 Severe to very severe disability A HAQ-DI score reduction by 0.22 represents the MCID.
hsCRP	Marker of systemic inflammation associated with disease activity in RA that is generally not detectable with routine CRP assays.
ITT population	Primary analysis population comprising all enrolled and randomized subjects.
PTE population	Subjects from ITT population who received the assigned treatment through Week 12, have no major procedural protocol deviations, and for whom follow-up data are available.
RA disease activity assessments	A standardized set of RA assessments that should be performed in the following order: • HAQ-DI • SGA • Subject's pain • TJC28 • SJC28 • EGA • hsCRP (mg/L)
RAMRIS	A standardized method for MRI acquisition of the hand and wrist, joint pathology definitions and a scoring system for semiquantitative evaluation of: • *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 • *CARLOS (cartilage loss)*. 25 joints each scored on a scale from 0 to 4, resulting in a total score from 0 to 100
Randomization	Process of randomly assigning subjects to a treatment or control group which occurs after completion of Day 0 assessments.

Term	Definition
Rescue treatment	Additional or change in treatment to address worsening of RA symptoms or failure to achieve adequate clinical improvement prior to Week 12. Additional treatments considered as rescue include: • Addition of a biologic or targeted synthetic DMARD • Dose increase of the ongoing conventional synthetic DMARD background therapy or addition of another conventional synthetic DMARD • Addition or dose increase of a corticosteroid (equivalent to an average daily use > 10mg prednisone/day between study visits) • A corticosteroid injection within 30 days of a study visit Subjects initiating rescue treatment prior to Week 12 will be imputed as non-responders in the analysis of primary and key secondary endpoints.
SADE	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. Anticipated SADE is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
SAE	Adverse events are considered "serious" if, in the view of either investigator or sponsor, they result in any of the following outcomes: • Death • A life-threatening illness or injury • Permanent impairment of a body structure or a body function • Inpatient hospitalization or prolongation of existing hospitalization • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, or • Fetal distress, fetal death, or a congenital anomaly/birth defect. • Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. [BS EN ISO 14155]
Safety population	All enrolled subjects.
SF-36	A survey of subject health with 36 questions in 8 domains: • Vitality • Physical functioning • Bodily pain • General health perceptions • Physical role functioning • Emotional role functioning • Social role functioning • Mental health The instrument's scores are norm-based: • 0 Maximum disability • 50 Average health status • 100 No disability

Term	Definition
	In addition, 2 global measures are derived: • PCS or physical component summary • MCS or mental component summary
SGA	Subject's global assessment of their RA disease activity using a NRS from 0 (inactive) to 10 (very active).
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.
Source documents	Original documents, data, and records. Printed, optical, or electronic documents containing source data.
Stratification	Allocation of subjects into treatment groups based on a characteristic that may affect trial outcome.
Subject	An individual who participates in a clinical investigation.
Subject's pain assessment	Subject's assessment of their RA-related pain using a NRS from 0 (no pain) to 10 (worst pain imaginable).
TJC28 & SJC28	A standardized assessment examining a total of 28 joints for signs of swelling and tenderness or pain 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).
Treatment to Open Label (TOL) population	Treatment subjects 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.
UADE	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. [21 CFR 812]
USADE	Any serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. [BS EN ISO 14155]
Use error	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. Use error includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error. [BS EN ISO 14155]
VNS	A medical treatment that involves delivering electrical impulses to the vagus nerve.

4 PROTOCOL SUMMARY

Study Title	Vagus Nerve Stimulation Using the SetPoint System for Moderate to Severe Rheumatoid Arthritis: The RESET-RA Study
Objective	To assess the safety and efficacy of the SetPoint System for the treatment of adult patients with active, moderate to severe rheumatoid arthritis (RA) who have had an inadequate response or intolerance to biologic or targeted synthetic Disease-Modifying Anti-Rheumatic Drugs (DMARDs)
Investigational Device	The SetPoint System
Phase	Phase 3 Pivotal
Study Design	An operationally seamless, 2-stage, randomized, sham-controlled, double-blind, multicenter pivotal study enrolling at least 240 and up to 250 subjects at up to 45 study centers across the U.S.: • **Stage 1** with approximately 60 randomized subjects at up to 25 study centers • **Stage 2** with approximately 190 randomized subjects at up to 45 study centers, including centers from Stage 1 There will be a pause in enrollment after enrollment in **Stage 1** is completed. This pause in enrollment is intended to allow completion of Week 12 assessments by 60 enrolled and randomized subjects and review of interim analysis results by the independent Data Monitoring Committee (DMC) and the U.S. Food Drug Administration (FDA). The DMC and FDA will confirm whether the study can advance to enroll subjects in **Stage 2**. After completing primary endpoint assessments at Week 12, there will be a one-way crossover of control subjects to active stimulation and a 252-week open-label follow-up with all subjects (treatment and control) receiving active stimulation to evaluate long-term safety. Blinding will be maintained until the last enrolled and randomized subject in Stage 2 completes Week 12 assessments, and the study dataset for primary analysis is locked. The initial, 12-week follow-up period will generate safety and efficacy data to support an application for Premarket Approval (PMA). The PMA application will also include supporting data on long-term safety for all subjects for whom long-term data are available at the time of application.
Study Procedures	• **Enrollment.** Subjects meeting all the inclusion and none of the exclusion criteria are considered enrolled once Implant Procedure is attempted. • **Implant Procedure.** Subjects meeting final eligibility will undergo placement of the SetPoint System in the neck, on the left cervical vagus nerve within the carotid sheath. The procedure will take place in an operating room under general anesthesia and be performed by surgeons trained and experienced in procedures involving implantation of vagus nerve stimulators. • **Randomization.** Within 14-21 days after Implant Procedure and after completing Day 0 assessments, subjects will be assigned randomly in a 1:1 ratio into either a treatment or control group using an interactive response technology. Randomization will be stratified by inadequate response or loss of response to Janus kinase inhibitors (JAKi); inadequate response or loss of response to ≥4 biological DMARDs (bDMARDs) with ≥ 2 mechanisms of action; and RA severity at Day 0. All subjects, investigators and site staff will remain blinded to the treatment assignment until the last subject in Stage 2 completes Week 12 follow-up assessments and the dataset for primary analysis is locked. • **Active & Non-active Stimulation.** Through Week 12, subjects assigned to the treatment group will receive active stimulation for 1 min once per day, and those

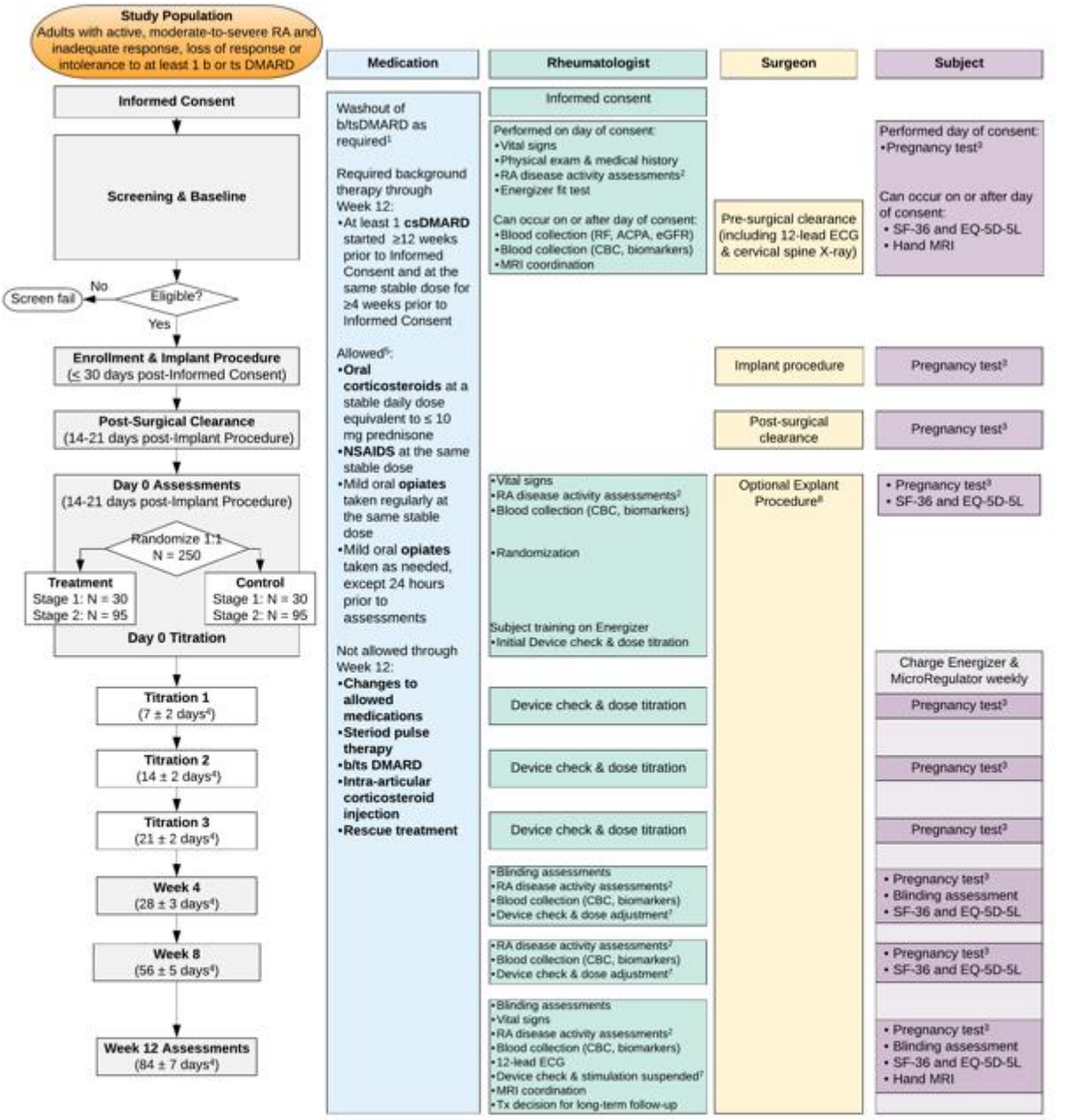
	assigned to the control group will receive non-active (sham) stimulation for 1 min once per day. After completion of Week 12 assessments, all subjects in the control group will crossover to active stimulation and all subjects (treatment and control) will receive active stimulation for 1 min once per day.
Study Population	Adults (22-75 years of age, inclusive) with active, moderate to severe RA despite ongoing treatment with a conventional synthetic DMARD who have had an inadequate response, loss of response or intolerance to 1 or more biologic or targeted synthetic DMARDs, including JAKi. *Note: Subjects with an inadequate response or loss of response to JAKi will be limited to 6 subjects*.
Eligibility Criteria	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 an inadequate response, loss of response, or intolerance to 1 or more biologic or targeted synthetic DMARDs, administered in accordance with their labels • 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 is acceptable, except during the 4 weeks preceding informed consent. Key exclusion criteria: • Current, regular use of nicotine-containing products. Subject does not agree to abstain from using nicotine-containing products throughout study participation. • Untreated or poorly controlled psychiatric illness or history of substance abuse • Significant immunodeficiency due to underlying illness • History of stroke or transient ischemic attack, or diagnosis of cerebrovascular fibromuscular dysplasia • Clinically significant cardiovascular disease • Neurological syndromes, including multiple sclerosis, Alzheimer's disease, or Parkinson's disease • Uncontrolled fibromyalgia • History of left or right carotid surgery • History of unilateral or bilateral vagotomy, partial or complete splenectomy • Recurrent vasovagal syncope episodes • Hypersensitivity/allergy to MRI contrast agents and/or unable to perform MRI
Primary Efficacy Endpoint	Difference between treatment and control groups in the proportion of subjects who achieve the ACR20 response at Week 12
Safety Evaluation	All adverse events reported by subjects between informed consent and Week 264 (end of study) will be tabulated.
Concomitant Medications	• All subjects (treatment and control) will be **required** to continue background therapy with at least 1 conventional synthetic DMARD started at least 12 weeks prior and at a stable dose for at least 4 weeks prior to informed consent. Dosage and type must remain stable through Week 12.

	• All subjects are **allowed** to use the following: Glucocorticoids at a stable dose equivalent to ≤ 10 mg/d of prednisone NSAIDs at a stable dose Mild oral opiates taken at a stable dose on a regular basis Mild oral opiates taken as needed, except 24 hours prior to assessments *Note: For the above medications, dose changes are **not allowed** through completion of primary endpoint assessments at Week 12. These medications should not be started before completion of Week 12 assessments in subjects that are not taking them at time of informed consent.* • All subjects (treatment and control) are **not allowed** to use biologic or targeted synthetic DMARDs from Implant Procedure through Week 12. • The application of **rescue treatment** is **not allowed** prior to completion of Week 12 assessments to allow sufficient time to evaluate clinical response to the investigational treatment compared to background therapy alone. Additional RA treatment is **allowed at any time** after completion of Week 12 assessments if the subject experiences worsening of RA symptoms or does not experience adequate clinical improvement. The decision about the need, type and timing of rescue treatment is left to the discretion of the Co-PI Rheumatologist and the subject. Rescue treatment shall be consistent with standard of care.
Follow-up	Each subject will return for **6 follow-up visits** through Week 12 (primary efficacy endpoint)**:** • Week 1, 2 and 3 for dose titration • Week 4, 8 and 12 for assessments After Week 12, each subject will return for **24 follow-up visits** through Week 264 (end of study): • Week 13, 14 and 15 for dose titration • Every 12 weeks from Week 24 through Week 264 for assessments Subjects may come in for **unscheduled office visits**, if necessary. Circumstances that may warrant additional visits include but are not limited to: RA-related adverse events requiring medical evaluation, device deficiency evaluation, device dose adjustment, suspending or resuming stimulation, or implant decommissioning.
Site's Roles and Responsibilities	**Rheumatology Site** **Co-Principal Investigator** • Responsible for all aspects of the study conduct at a given site • IRB oversight • Informed consent process • Screening & follow-up assessments • Complete a blinding assessment • AE and device deficiency reporting **Surgery Site** **Co-Principal Investigator** • Pre-surgical clearance • Surgical informed consent, if applicable • Implant procedure • Post-surgical clearance • AE and device deficiency reporting • Explant procedure, if applicable •

	Research Coordinator • Data entry into eCRF & query resolution • Maintenance of regulatory & subject binders • Visit coordination • MRI coordination • IRB reporting • Subject IFU & Energizer training • Device check & programming (dose titration & adjustment) • Questionnaire administration • Blood draws • Transfer of applicable screening records for surgeon's review • Device accountability **Joint Evaluator** • Perform joint & global assessments • Complete a blinding assessment	**Research Coordinator** • Coordination of pre- & post-Surgical Clearance, Implant Procedure • Transferring source worksheets and hospital records to the paired rheumatology site • AE and device deficiency reporting to the paired rheumatology site • Device accountability, if stored at hospital
Duration of Study Period	For a given subject in Stage 1 and Stage 2, the maximum study duration is 1,899 days (about 5 years): • 30 days from informed consent to Implant Procedure • 21 days between Implant Procedure and randomization at Day 0 • 84 days (about 3 months) between initiation of stimulation at Day 0 and Week 12 (primary endpoint) • 1,764 days (about 4.5 years) between Week 12 and Week 264	

5 STUDY FLOW DIAGRAM

5.1 Informed Consent to Week 12 (Primary Endpoint)



Abbreviations: b/ts, biologic/targeted synthetic; cs, conventional synthetic; DMARD, Disease-modifying anti-rheumatic drug; ECG, electrocardiogram; MRI, magnetic resonance imaging; Tx, treatment

[1] Subjects may consent pre-washout, during washout, or post-washout. Required minimum washout period (**Appendix A**) must be complete prior to undergoing Implant Procedure.

[2] RA disease activity assessments include: Health Assessment Questionnaire Disability Index (HAQ-DI), subject's global assessment, subject's pain assessment, tender and swollen joint counts, evaluator's global assessment, and hsCRP.

[3] Pregnancy test for female subjects of childbearing potential.

[4] From Day 0 (Randomization).

[5] Initiation or change in dosage is not allowed through Week 12 assessments.

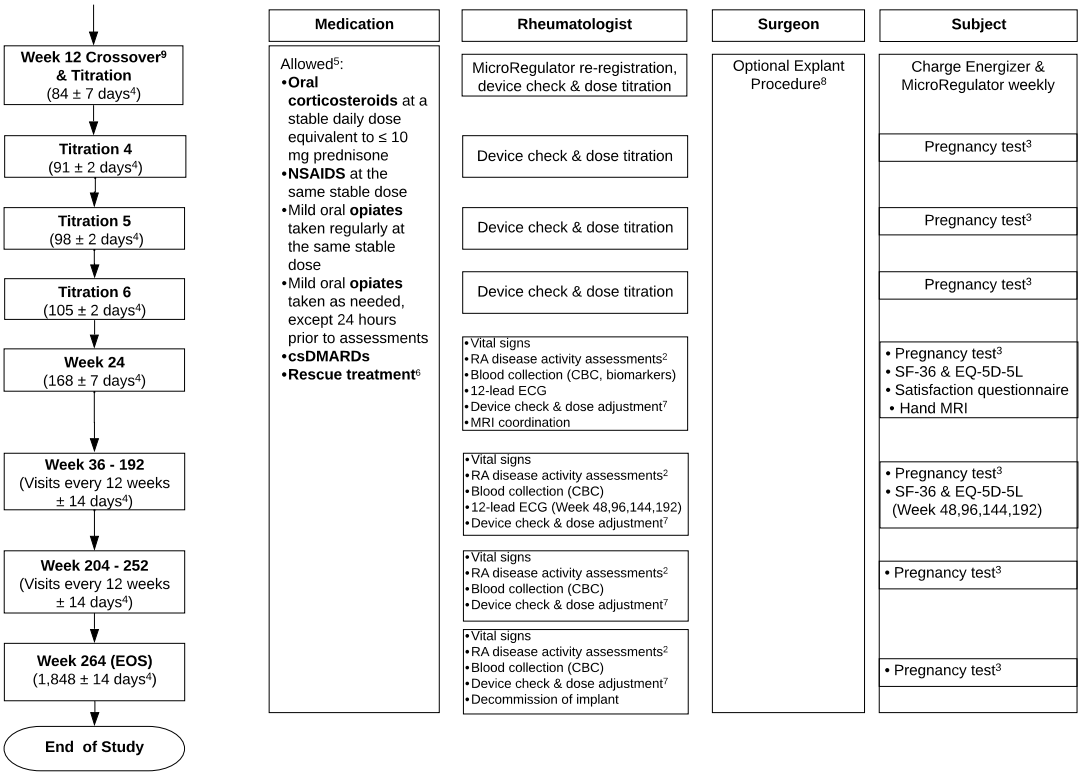
[6] The decision about the type and timing of rescue treatment is left to the discretion of the Co-PI Rheumatologist and the subject. Subjects that receive rescue treatment are expected to continue adhering to the study follow-up visit schedule, all study procedures, and will be monitored for safety.

[7] Dose adjustment only if required.

[8] Explant Procedure is optional and can happen at any time if the subject wants or needs to have their implant removed. Will require pre- and post-op clearance.

[9] One-way cross-over of control subjects to active stimulation.

5.2 Long-Term Follow-up



Abbreviations: b/ts, biologic/targeted synthetic; cs, conventional synthetic; DMARD, Disease-modifying anti-rheumatic drug; ECG, electrocardiogram; MRI, magnetic resonance imaging; Tx, treatment

[1] Subjects may consent pre-washout, during washout, or post-washout. Required minimum washout period (**Appendix A**) must be complete prior to undergoing Implant Procedure.
[2] RA disease activity assessments include: Health Assessment Questionnaire Disability Index (HAQ-DI), subject's global assessment, subject's pain assessment, tender and swollen joint counts, evaluator's global assessment, and hsCRP.
[3] Pregnancy test for female subjects of childbearing potential.
[4] From Day 0 (Randomization).
[5] Initiation or change in dosage is not allowed through Week 12 assessments.
[6] The decision about the type and timing of rescue treatment is left to the discretion of the Co-PI Rheumatologist and the subject. Subjects that receive rescue treatment are expected to continue adhering to the study follow-up visit schedule, all study procedures, and will be monitored for safety.
[7] Dose adjustment only if required.
[8] Explant Procedure is optional and can happen at any time if the subject wants or needs to have their implant removed. Will require pre- and post-op clearance.
[9] One-way cross-over of control subjects to active stimulation.

6 SCHEDULE OF ASSESSMENTS

6.1 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)	**Titration 1** (7 ± 2d[2])	**Titration 2** (14 ± 2d[2])	**Titration 3** (21 ± 2d[2])	**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	X	X	X
RA disease activity assessments[1]	X*			X				X	X	X
RA prior and current medication	X*									
Energizer 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						
Subject training on the use of Energizer				X						
Device check & dose titration				X	X	X	X			X [3]
Device check & dose adjustment if needed								X	X	
Blinding assessment [4]								X		X
Treatment decision for long-term follow-up										X
Device deficiency reporting		X	X	X	X	X	X	X	X	X
Adverse event reporting	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	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, subject'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 subject's initial eligibility and baseline values for the primary and key secondary efficacy endpoints.

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

[2] From Day 0 (randomization).

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

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

6.2 Long-Term Follow-Up

Assessment	Titration 4 (91 ± 2d[2])	Titration 5 (98 ± 2d[2])	Titration 6 (105 ± 2d[2])	Week 24 (168 ± 7d[2])	Week 36 (252 ± 14d[2])	Week 48 (336 ± 14d[2])	Week 60 (420 ± 14d[2])	Week 72 (504 ± 14d[2])	Week 84 (588 ± 14d[2])	Week 96 (672 ± 14d[2])	Week 108 (756 ± 14d[2])	Week 120 (840 ± 14d[2])	Week 132 (924 ± 14d[2])	Week 144 (1,008 ± 14d[2])	Week 156 (1,092 ± 14d[2])	Week 168 (1,176 ± 14d[2])	Week 180 (1,260 ± 14d[2])	Week 192 (1,344 ± 14d[2])	Week 204 (1,428 ± 14d[2])	Week 216 (1,512 ± 14d[2])	Week 228 (1,596 ± 14d[2])	Week 240 (1,1680 ± 14d[2])	Week 252 (1,764± 14d[2])	Week 264 (1,848 ± 14d[2]) (End of Study)
Vital signs				X	X	X	X	X	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	X	X	X	X	X	X	X	X
RA disease activity assessments[1]				X	X	X	X	X	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	X	X	X	X	X
Blood collection (biomarkers)				X																				
Hand MRI				X																				
12-lead ECG				X		X				X				X				X						
Device check & dose titration	X[3]	X[3]	X[3]																					
Device check & dose adjustment if needed				X	X	X	X	X	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	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	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	X	X	X	X	X	X	X	X

Abbreviations: CBC, complete blood count; d, day; EGA, evaluator's global assessment; HAQ-DI, Health Assessment Questionnaire Disability Index; hsCRP, high-sensitivity C-reactive protein; MRI, magnetic resonance imaging; RA, rheumatoid arthritis; SGA, subject's global assessment; SJC, swollen joint count; TJC, tender joint count.

[1] RA disease activity assessments include: HAQ-DI, SGA, subject's pain assessment, TJC28, SJC28, EGA, and hsCRP. Subjects must have ≥ 4TJC28 and ≥ 4SJC28 at consent to be eligible.
[2] From Day 0 (randomization).
[3] Dose titration is not performed if subject and Co-PI Rheumatologist decide that subject should not receive active stimulation in open-label, long-term follow-up period.

7 BACKGROUND INFORMATION

7.1 Rheumatoid Arthritis, Treatment Options and Unmet Clinical Need

Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with progressive joint damage, disability and systemic complications. RA has a prevalence of 0.5-1.0% of the population in developed countries. Reports of incidence range from 5 to 50 per 100,000 patient-years. The typical age of onset is between 40 and 50 years, and women are affected three times more commonly than men (Smolen 2016).

RA is characterized by chronic joint inflammation that leads to permanent structural damage. Multiple joints are involved, typically in a symmetrical pattern. Systemic inflammation with elevated circulating levels of cytokines and other inflammatory mediators is accompanied by autoantibodies such as rheumatoid factor (RF), and anti-citrullinated peptide antibodies (ACPA). Chronic inflammation of the synovial lining of the joint leads to joint cartilage damage, formation of an inflammatory infiltrate termed a “pannus” and erosions of the peri-articular bone. With time, these processes result in physical deformity of the joint, loss of physical function, and eventual debility (McInnes 2010).

In some patients, RA causes extra-articular inflammation of the pulmonary, dermatologic, nervous, and other organ systems that can be severe. The effect of systemic inflammation on the vascular system makes RA an independent risk factor for early and accelerated atherosclerosis, with elevated cardiovascular morbidity and mortality. This risk is further increased in patients whose disease remains active despite treatment (Nurmohamed 2015). Studies have suggested that RA patients with these extra-articular manifestations, as opposed to RA patients without them, have an increased mortality when compared with the general population (Turesson 2004, Turesson 2002). On average, the established RA patient has two or more comorbid conditions (Michaud 2007). Respiratory disease and cardiovascular disease mortality were both significantly elevated for women with RA.

Many of the extra-articular manifestations of RA are associated with increased disease activity and with markers of inflammation, such as high levels of RF and C-reactive protein (CRP) (Baecklund 2006, Hannawi 2007, Jonsson 1995, Turesson 2007). This suggests that if RA is treated effectively, long term joint damage and disability might be avoided, and the comorbid impact of extra articular systemic inflammation might be attenuated. The risks of permanent disability and increased mortality support the need for novel therapies as options for patients who have not responded to or who are intolerant to currently available treatments.

Current treatments of RA involve the early use of several older synthetic agents known as conventional synthetic Disease-Modifying Anti-Inflammatory Drugs (DMARDs). Over the past 20 years, a number of newer, targeted protein therapeutic biologic DMARDs have been developed. In 2013 the first oral targeted synthetic DMARD, tofacitinib, was introduced. Biologic

or targeted synthetic DMARDs are typically begun once the patient has demonstrated an incomplete clinical response (IR) to one or more conventional synthetic DMARDs.

Effectiveness of current treatment options often diminishes over time (Kalden 2017) and adverse events frequently emerge. As a result, a number of patients are unable to tolerate or fail to respond to available therapies for managing their disease. Failure to respond to targeted therapies is a complex process that involves both primary failure, secondary failure after loss of initial response and intolerance to the AE profile secondary to immunosuppression and infectious complications. Factors contributing to failure to respond include inadequate drug concentrations, presence of neutralizing anti-drug antibodies, AEs, and lack of compliance and persistence with drug therapy.

The development of targeted therapies was a breakthrough that has resulted in substantial improvement in the care of RA and has greatly reduced long-term disability from the disease. However, aside from loss of effectiveness, these drugs are very costly and are associated with uncommon but severe and often life-threatening side effects (Chen 2018, Singh 2012). Thus, there clearly remains a significant unmet medical need in RA.

Despite the availability of conventional synthetic DMARDs such as methotrexate, leflunomide and sulfasalazine and multiple biologic DMARDs such as TNF inhibitors (TNFi), up to 40% of RA patients fail to reach low disease activity and only about one-third of established RA patients meet the criteria for clinical remission (Haugeberg 2015). Adverse events associated with therapy, long-term non-compliance, and high cost are partially responsible for the low rates of response to treatment. Patients who have failed a particular mode of therapy, such as a TNFi, can switch to a mechanistically different mode, such as IL-6 inhibition, B-cell depletion or use of targeted synthetic DMARDs. However, despite switching to drugs with an alternative mode of action, only 30% of patients achieve low disease activity or clinical remission after the treatment switch. Furthermore, use of biologic and targeted synthetic DMARDs may increase the rate of infection with viruses such as *H zoster* (shingles) and may predispose patients to rare and potentially fatal disorders, such as progressive multifocal leukoencephalopathy.

Therefore, there is an unmet medical need for alternative therapies for patients who fail to respond to or are intolerant of approved targeted agents. A medical device may offer a useful, alternative solution to patients, caregivers and healthcare payers.

7.2 Investigational Device

7.2.1 Intended Use

The SetPoint System is indicated for the treatment of adult patients with active, moderate to severe RA who have had an inadequate response or intolerance to 1 or more biologic or targeted synthetic DMARDs.

7.2.2 Mechanism of Action

The mechanism of action of the SetPoint System is based on electrical activation of the cholinergic anti-inflammatory pathway, or CAP (**Figure 1**) (Tracey 2002). Specifically, the SetPoint System activates the efferent arm of the inflammatory reflex, a highly conserved endogenous mechanism used by the central nervous system to detect infection and injury and coordinate the inflammatory response (Andersson 2012a, Andersson 2012b).

The discovery that cholinergic neurons inhibit acute inflammation has expanded the understanding of how the nervous system modulates immune responses and represents a potential paradigm shifting approach to the management of RA. The SetPoint System has been designed to specifically modulate the CAP to treat autoimmune diseases using completely novel, application-specific electrical pulse parameters delivered by an implantable neurostimulator with a unique physical form factor.

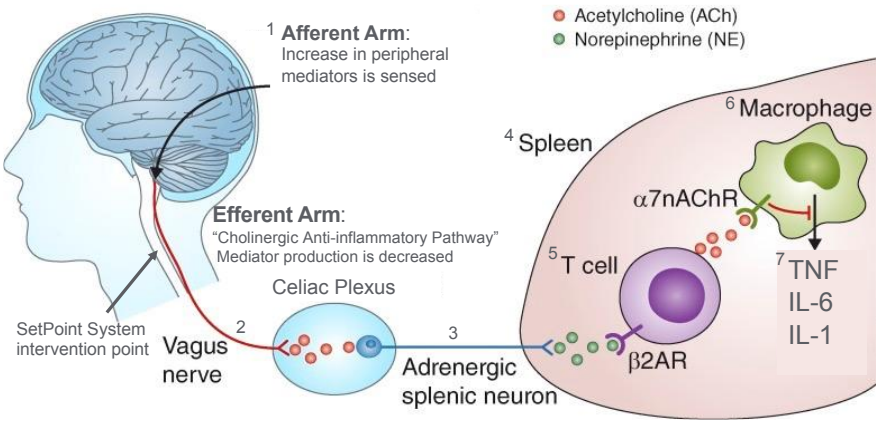


Figure 1: Stimulation of the Cholinergic Anti-Inflammatory Pathway

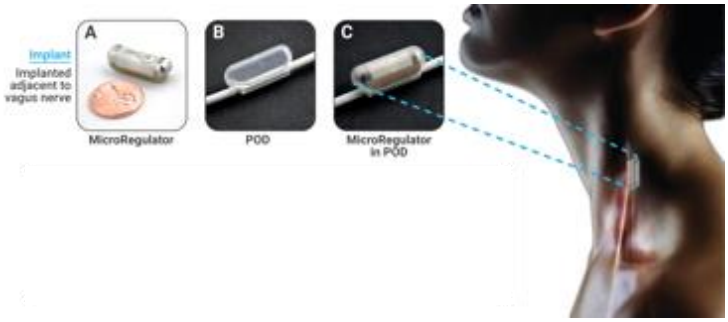
Since the feasibility of restricting systemic inflammation through electrical stimulation of the vagus nerve was first demonstrated 20 years ago (Borovikova 2000), several key findings about the neural and molecular specificities of this pathway have been elucidated by multiple researchers. In this reflex (**Figure 1**), cytokines are sensed in the periphery and cytokine-specific signals travel up the vagus nerve and enter the sensory nuclei in the brain stem (Steinberg 2016). Anti-inflammatory signals are then reflexively sent down the efferent vagus nerve, through the CAP (Tracey 2002), and this is the ideal intervention point for a neuromodulation-based therapy. Selective lesioning experiments in preclinical studies have demonstrated that the anatomical path of the CAP is hardwired through the subdiaphragmatic vagus nerve, across the celiac plexus, through the splenic nerve and into the spleen.

The splenic nerve releases norepinephrine into the white pulp of the spleen, where it acts locally on β-adrenoceptors on the cell surface of a highly specialized subset of resident T cells that express choline acetyltransferase (ChAT+), the rate limiting enzyme in the production of acetylcholine (ACh). These T cells then produce and release ACh for at least 30 minutes (Rosas-

Ballina 2011), a highly disparate timeframe from acetylcholine release within a typical nervous synapse. The ACh binds the α7 nicotinic ACh receptor (α7nAChR) expressed on the resident macrophages, leading to a reduced production of several key proinflammatory mediators. Fundamental to activating this pathway in treating RA, ACh released by ChAT+ T cells also act on resident B cells and circulating immune cells that traverse the spleen, leading to phenotypic changes in T cells, monocytes, and neutrophils, thereby decreasing inflammatory infiltrates at distant sites of inflammation such as the joints in RA (Huston 2009, Karimi 2010, Koopman 2016, Mina-Osorio 2012, Nizri 2009). Importantly, as the SetPoint System activates endogenous signal transduction pathways, key cytokines are reduced but not eliminated to a complete loss of bioavailability, allowing for competent immunosurveillance. Indeed, electrical stimulation of the vagus nerve increases levels of pre-resolving mediators that directly act on phagocytes to both reduce proinflammatory cytokines and to enhance microbial killing and clearance (Dalli 2017, Serhan 2018).

7.2.3 Description of the SetPoint System

The SetPoint System comprises 2 implantable parts (MicroRegulator, Positioning and Orientation Device or POD, **Figure 2**), and 2 external parts (Energizer, Prescription Pad).



A) MicroRegulator, B) Positioning and Orientation Device (POD), C) MicroRegulator inside of POD and its placement on the left cervical vagus nerve

Figure 2: SetPoint System Implantable Components

MicroRegulator

The surgically implanted MicroRegulator functions as a pulse generator with an integrated lead. The vagus nerve fits into a groove in the saddle-like base of the MicroRegulator, and the electrodes in the groove are thereby brought into close apposition to the nerve for efficient stimulation (**Figure 2**). An onboard microcontroller unit and an application-specific integrated circuit control MicroRegulator. MicroRegulator is powered by a rechargeable lithium-ion battery with Zero Volt™ technology. A ferrite core antenna mounted on the hybrid printed circuit board assembly provides links for telemetry and radio frequency-induced battery recharging.

MicroRegulator delivers symmetric, current-limited, charge-balanced bipolar pulses. It is approximately 2.5 cm in length and 2.6 g in weight.

The MicroRegulator settings chosen for this study are based on extensive clinical experience with the VNS Therapy™ System (Cyberonics Inc., Houston, TX, USA [PMA P970003]), which is indicated for epilepsy and depression, clinical studies performed with the Cyberonics VNS Therapy System for treatment of RA (SPM-005 and SPM-006), and preclinical and RA clinical studies with the SetPoint System (SPM-008). Stimulation pulse parameters that modulate vagus nerve firing and elicit CAP response include output current, pulse frequency, pulse duration, and duty cycle (on time/off time). The protocol-specified settings for MicroRegulator are provided in **Table 1**.

Table 1: Microregulator Stimulation Pulse Parameters

Parameter	Value
Output current	0 - 2.5 mA
Pulse frequency	10 Hz
Pulse duration	250 µs
Duty cycle	1 min once per day

POD

The surgically implanted POD is a flexible silicone enclosure that holds MicroRegulator and the vagus nerve together, maintaining the vagus nerve in a cradled position within the electrode groove on MicroRegulator. POD also electrically insulates MicroRegulator from surrounding tissues.

Energizer

Energizer is a non-implanted, externally worn collar powered by a lithium-ion battery. Integrated into Energizer is a coil running circumferentially, serving to transmit and receive telemetry information to and from MicroRegulator. Information transmitted includes the prescribed stimulation frequency, duration and intensity. Information received includes performance and compliance data. Energizer is also used to transmit radiofrequency energy to the MicroRegulator antenna for inductive battery charging. Energizer is positioned on the subject's neck and secured with a magnetic closure. Energizer has a single outward facing visual indicator (a multi-color LED), an audio output (speaker), and an accelerometer (touch input) all of which serve as an interface for control of various Energizer and MicroRegulator functions. Energizer only needs to be worn for specific operations, i.e., programming MicroRegulator stimulation parameters, checking MicroRegulator performance and compliance, and recharging. Energizer is provided with a Wireless Charger used to charge Energizer whenever it is not in use.

Prescription Pad

Prescription Pad is an Apple iPad application for SetPoint Medical's proprietary user interface (UI) software with standard iOS touchpad controls. Prescription Pad communicates with Energizer through the onboard Apple Bluetooth hardware. Prescription Pad serves as the interface between the clinician and MicroRegulator and is used by clinicians only (not subjects) to adjust stimulation strength. It is also used to collect information on MicroRegulator performance and compliance.

7.3 Summary of Prior Clinical Experience

7.3.1 Proof-of-concept studies using the VNS Therapy System

SetPoint Medical conducted a proof-of-concept clinical study (SPM-005) with long-term follow-up (SPM-006) using the VNS Therapy System, which was first approved in Europe in 1994 and in the U.S. in 1997 for medically refractory epilepsy. Unlike the implanted components of the SetPoint System which are configured as a single, self-contained unit that functions as a pulse generator with integrated leads, the VNS Therapy System consists of a separate pulse generator that is implanted in a subcutaneous, subclavicular pocket with a lead that runs from the generator to the neck where electrodes are applied to the vagus nerve (**Figure 3**). For the purpose of the proof-of-concept studies, the pulse characteristics of the VNS Therapy System were modified, and the device considered investigational because it was used outside the labeled indications.

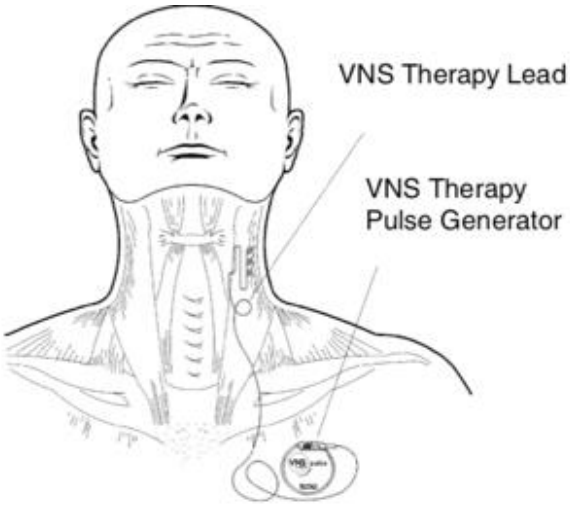


Figure 3: Cyberonics VNS Therapy System

SPM-005 was a single-arm, open-label, pilot study in 18 adult patients with active, moderate to severe RA, who had experienced an insufficient response to methotrexate (Cohort I) or to methotrexate and at least 2 different types of biologic DMARD therapy (Cohort II). The study was conducted at 4 sites in Europe (1 in the Netherlands, 1 in Croatia, 2 in Bosnia) between August 2011 and May 2014. The objective was to evaluate the safety and efficacy of VNS for treatment of RA by using a modified version of the Cyberonics VNS Therapy System. The study

design is depicted in **Figure 4**. On the first treatment day (study Day 0), subjects received a single dose of stimulation lasting 60s with electric current pulses of 250 µs duration at 10 Hz and an output current between 0.25–2.0 mA, as tolerated. No further stimulation was delivered for 7 days. On study Day 7, the output current was adjusted to the highest amperage tolerated, up to 2.0 mA; and this level of current was subsequently delivered once daily for 60 s in 250 µs pulse widths at 10 Hz. Current escalation up to the highest tolerated amperage (up to 2.0 mA) was repeated weekly until Day 28. At that visit, the frequency of daily stimulation events was increased to 4 times daily in patients who had not achieved a moderate or good clinical response according to EULAR criteria. Daily stimulation was continued until the primary endpoint at Day 42. Stimulation was discontinued for 14 days and then restarted from Day 56 to Day 84. Subjects who completed SPM-005 were enrolled in SPM-006.

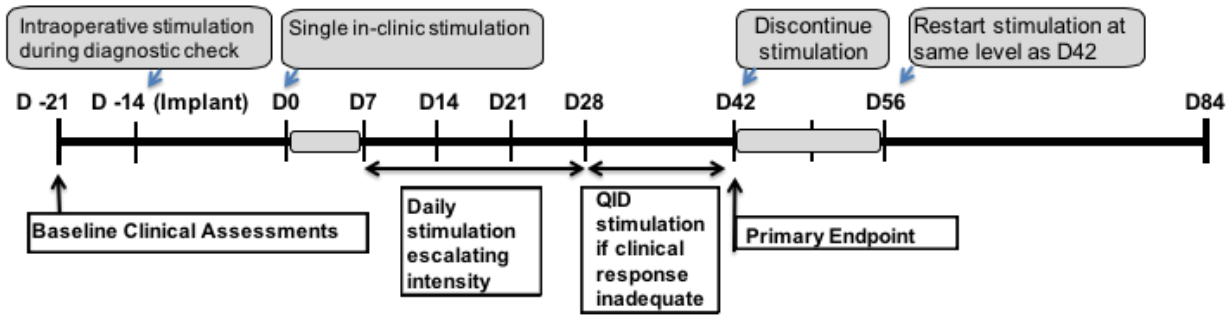
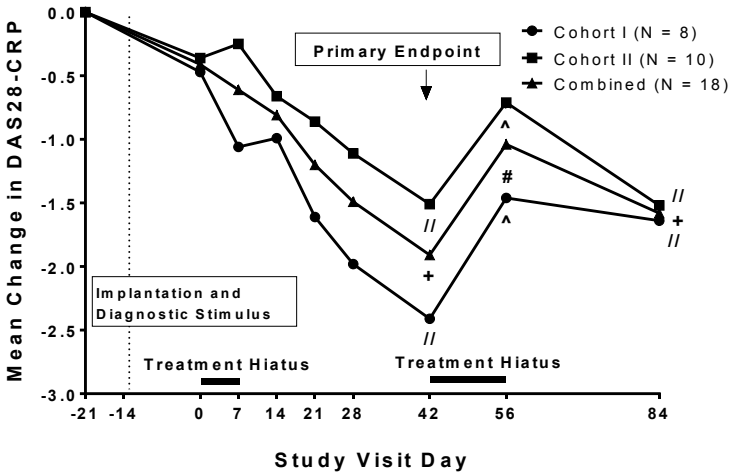


Figure 4: SPM-005 Study Design

Eighteen subjects were implanted, and 17 included into the efficacy analysis. All patients continued to use methotrexate (≤ 25 mg weekly). The mean age was 51 years (range 36-69), 78% were female, 94% were Caucasian, and mean RA duration was 11 years (SD 5.9). At Day 42, the mean DAS28-CRP score was reduced by 2.41 in Cohort I, 1.51 in Cohort II, and 1.91 overall from 5.99 (0.77) at baseline (**Figure 5**). Escalation to 4 times daily stimulation at Day 28 was necessary in 3 out of 8 subjects in Cohort I and in 6 out of 10 subjects in Cohort II.

There were no deaths, serious AEs, withdrawals from the study because of AEs, opportunistic infections or implanted device infections observed in either cohort. In agreement with known risks of the procedure, 9 subjects experienced mild or moderate AEs associated with implanting the VNS on the left cervical vagus nerve. The reported AEs were typical to those seen with the implantation of the Cyberonics VNS Therapy system (Koopman 2016).



p < 0.05 vs. day -21, //p < 0.01 vs. day -21,+p < 0.001 vs. day -21, # p < 0.001 vs. day 42, ^p < 0.05 vs. day 42

Figure 5: SPM-005 DAS28-CRP Change from Baseline

The SPM-005 results demonstrated that the use of VNS was well tolerated and resulted in clinically meaningful improvement among multi-drug refractory RA patients. The ACR20 response rate in the subset of subjects who had failed ≥ 4 biologic DMARDs with ≥ 2 mechanisms of action compares favorably with those reported in the JAKi trials (**Figure 6**) and represents a reasonable expectation that the VNS therapy could provide a valid alternative to JAKi patients.

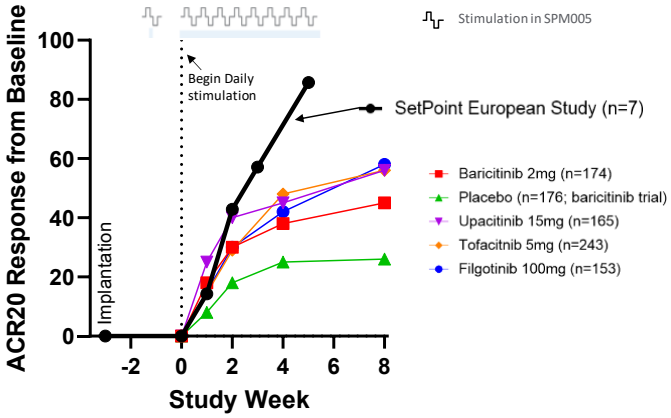


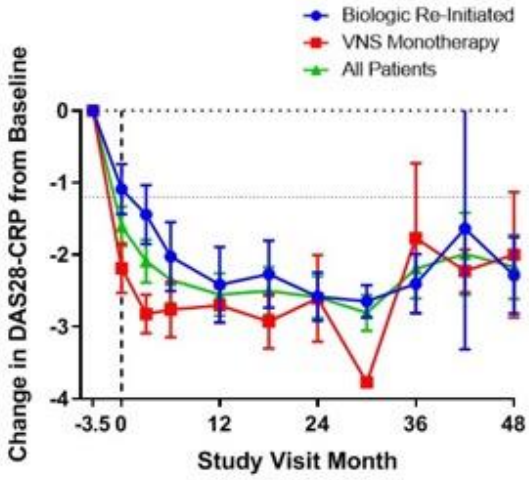
Figure 6: SPM-005 ACR20 Response in Subjects with ≥ 4 Prior bDMARDs Compared to JAKi Trials

After completing SPM-005, all subjects were enrolled into SPM-006, an open-label, long-term observational study, and were followed until the final enrolled patient had completed 48 months in the study. In SPM-006, investigators were allowed to initiate biologic DMARDs at their discretion. SPM-006 also allowed the exploration of a variety of stimulation schedules, self-administered by subjects, without any control over the number of stimulations sessions per day or the duration of each session. A review of site comments in the database showed that several patients did not fully comply with daily treatment. Of the 18 subjects enrolled, 4 subjects

discontinued prior to their Month 48, and 3 more discontinued after their month 48 but prior to the end of study. Two subjects discontinued from the study because of TEAEs (Medical Device Discomfort 2 years after stimulations began, and Whipple's Disease 5 years after stimulations began). The other 5 withdrew for subject-defined reasons.

All efficacy analyses were repeated for 2 subgroups: those who had biological treatment re-introduced, and those who did not have biological treatment re-introduced (also called VNS monotherapy). The efficacy analysis was also repeated separately for Cohort I and Cohort II. The primary efficacy endpoint was the change in DAS28-CRP. However, analysis of the DAS28-CRP in the latter months of the study was hampered by sites not collecting CRP levels, which are needed to calculate the DAS28-CRP. Therefore, a post hoc analysis was added for the standard, validated metric known as the Clinical Disease Activity Index (CDAI), because the CDAI calculation does not include CRP.

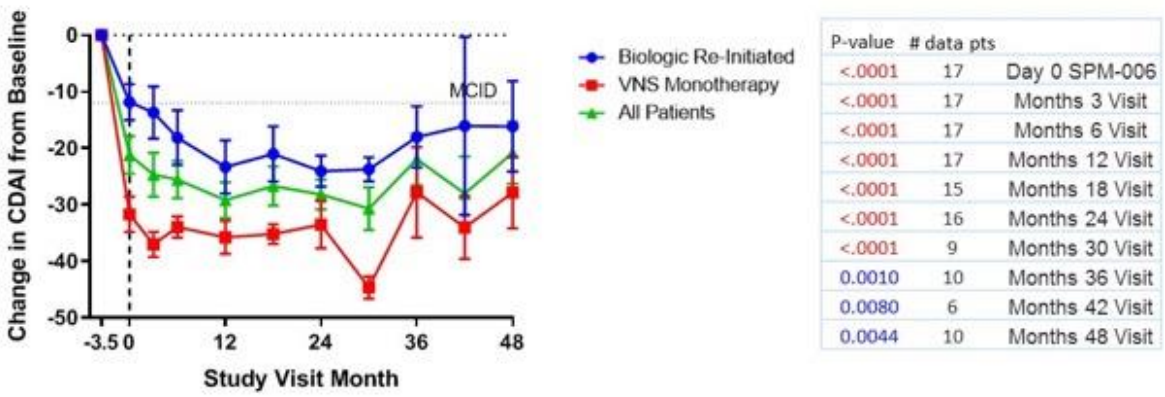
The primary efficacy endpoints were therefore the change in CDAI and DAS28-CRP from baseline 1 (Screening visit of base study SPM-005) and baseline 2 (Day 0 of SPM-006) to each follow-up visit. The time course of the average change in the DAS28-CRP is plotted in **Figure 7**. In this figure the MCID of -1.2 is indicated by the light blue dotted horizontal line. The average change in DAS28-CRP for the All Subjects group remained significantly reduced from baseline 1 (shown as Study Visit Month -3.5) throughout 48 months of follow-up. The group that remained on VNS monotherapy had a larger reduction in DAS28-CRP from baseline 1 than the group that re-initiated biologic therapy.



P-value	# data pts	Study Visit Month
<.0001	17	Day 0 SPM-006
<.0001	17	Months 3 Visit
<.0001	16	Months 6 Visit
<.0001	17	Months 12 Visit
<.0001	14	Months 18 Visit
<.0001	14	Months 24 Visit
<.0001	7	Months 30 Visit
0.0007	9	Months 36 Visit
0.0256	5	Months 42 Visit
0.0009	10	Months 48 Visit

Figure 7: SPM-005/006 DAS28-CRP Change from Baseline

The time course of the average change in the CDAI is plotted in **Figure 8**. The MCID of -12 is indicated by the light blue dotted horizontal line. The CDAI was significantly decreased from baseline 1 (shown as Month -3.5) at the start of SPM-006 and remained decreased throughout 48 months of follow-up.



P-value	# data pts	
<.0001	17	Day 0 SPM-006
<.0001	17	Months 3 Visit
<.0001	17	Months 6 Visit
<.0001	17	Months 12 Visit
<.0001	15	Months 18 Visit
<.0001	16	Months 24 Visit
<.0001	9	Months 30 Visit
0.0010	10	Months 36 Visit
0.0080	6	Months 42 Visit
0.0044	10	Months 48 Visit

Figure 8: SPM-005/006 CDAI Change from Baseline

Adverse events were recorded from the time of enrollment through end of study. There were no deaths in this study. Nine subjects experienced an SAE, but only 1 SAE was deemed to be device related. The device related TEAE was device pain and discomfort, which ranged from mild to moderate in severity. All 18 subjects reported at least 1 TEAE during the study. There were no significant findings based on review of vital signs, physical examination or other observations in this study.

In conclusion, in this group of RA patients, VNS applied with the Cyberonics VNS Therapy System resulted in clinically important improvements in DAS28-CRP within several months of treatment initiation that was maintained over 48 months of follow-up. These improvements were observed for subjects that previously had an insufficient response to targeted biological therapies, as well those that had an insufficient response to conventional synthetic DMARDs. The addition of adjunctive therapy to biologic DMARD-refractory subjects with only partial response with VNS alone enabled several subjects to achieve low disease activity. Surprisingly, low disease was achieved in the 2 subjects who were prescribed the same biologic DMARD that they had previously failed as co-therapy to VNS, as if VNS had re-sensitized the patients to those drugs. The ability to add a biologic as an adjunctive therapy in patients that do not reach low disease is a unique and potentially very important aspect to VNS therapy.

7.3.2 Pilot RCT using the SetPoint System

Encouraged by the results generated in the proof-of-concept studies with the Cyberonics VNS System, SetPoint developed its own implantable VNS system to treat patients with drug-refractory RA. The SetPoint System is a miniaturized stimulator, with the electrodes and pulse generator integrated into a single component that is implanted directly on the nerve. The procedure to implant this device requires a single incision and is less invasive compared to the Cyberonics VNS System.

SPM-008 was the first-in-human pilot study of the SetPoint System. The study enrolled 14 adult patients with active, moderate to severe RA and an incomplete response or intolerability to at least 2 biologic and/or targeted synthetic DMARDs having at least 2 different mechanisms of action.

The study was conducted from March 2018 to December 2018 at 4 sites in the U.S. The objective was to evaluate the safety and efficacy of the SetPoint System for the treatment of RA. Subjects who completed SPM-008 were enrolled in a long-term extension study (SPM-011), which is currently ongoing.

The study was conducted in 2 stages. Stage 1 (N = 3) was open-label, and Stage 2 (N = 11) was randomized, sham-controlled, blinded trial. All subjects in Stage 1 received a single dose of stimulation lasting 1 min, QD. Once all subjects in Stage 1 completed 1 week of VNS treatment, a Safety Review Team reviewed all available individual and aggregate safety data and recommended initiation of Stage 2 enrollment. The subjects in Stage 2 were randomized 1:1:1 into 1 of 2 active device groups (1 min QD or 1 min QID) or a sham group (device is implanted but is not activated: 0 min QD). Three subjects were randomized to treatment QD, 4 subjects were randomized to treatment QID, and 4 subjects were randomized to sham. The study design is depicted in **Figure 9**.

Screening clinical assessments of subjects were performed during the Week -6 Visit, and an inactive VNS system was implanted under general endotracheal anesthesia at the Week -2 Visit. The subjects then recovered from surgery for at least 14 days. At Day 0, after completing baseline assessments and randomization, subjects began daily stimulation (1 min QD, 1 min QID, or 0 min QD). Electric current pulses were 250 µs duration at 10 Hz with an output current between 0.25–2.5 mA, which was increased up to the highest tolerated amperage, or upper comfort level (UCL, up to 2.5 mA) on a weekly basis until Week 5.

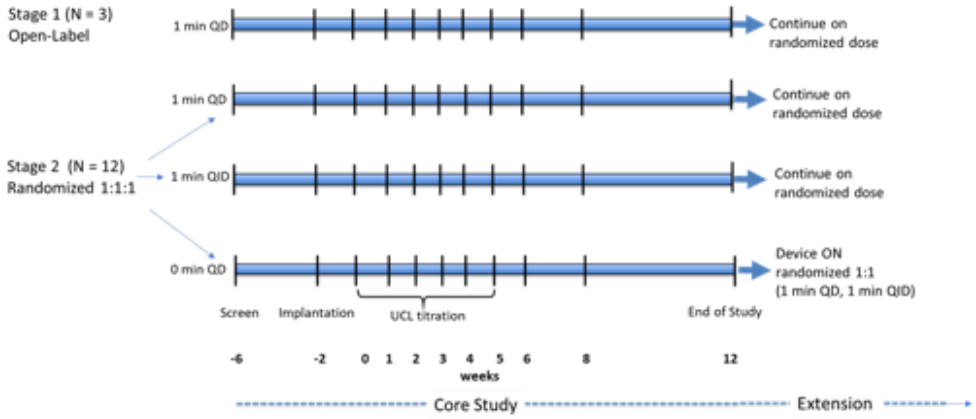


Figure 9: SPM-008 Study Design

Fourteen patients were implanted and continued to use a conventional synthetic DMARD throughout participation. The mean age was 51 years (range 26-73), and the majority of subjects were female (78%) and Caucasian (86%) with average RA duration of 14 years (SD 11.4). The DAS28-CRP score at baseline was 5.5 (SD 1.9). The primary efficacy endpoint was change in DAS28-CRP score from baseline to Week 12 (end of study) and is shown in **Figure 10**.

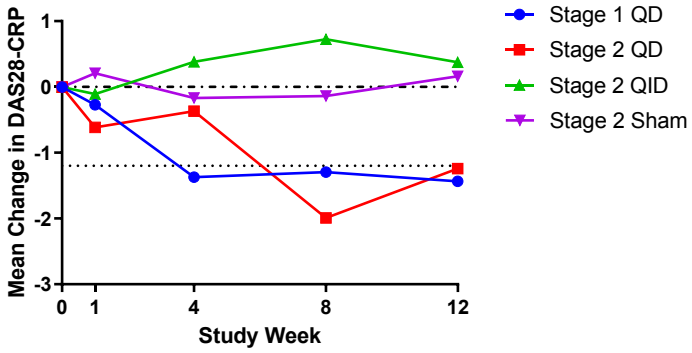


Figure 10: SPM-008 DAS28-CRP Change from Baseline

The mean change in CDAI from Day 0 baseline is plotted in **Figure 11**. Both Stage 1 and 2 QD groups exceeded MCID in the CDAI metric at 12 weeks, based on the change from the Day 0 baseline. In the sham group, 0 subjects exceeded the MCID in the CDAI metric at 12 weeks.

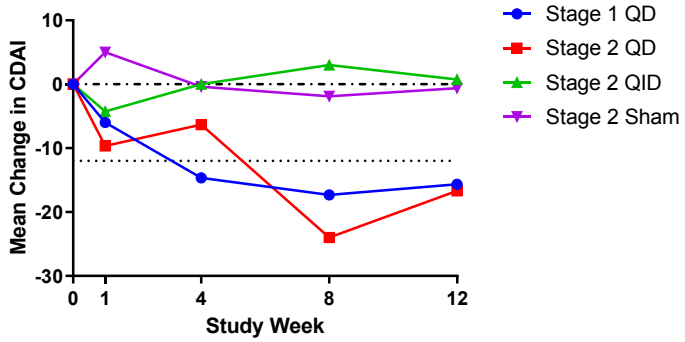


Figure 11: SPM-008 CDAI Change from Baseline

The subjects enrolled in SPM-008 had previously failed on average 5 different agents with nine (9) of 14 having failed a JAKi as well. It is well established that the more biologic agents that an RA patient had previously failed, the lower the expected clinical response rate will be for the next drug used to treat active disease. Fifty percent of these highly drug-refractory subjects receiving VNS with the SetPoint System showed clinically meaningful improvements within 12 weeks of stimulation.

There were no deaths, device-related AEs, AE-related withdrawals, opportunistic infections or implanted device infections observed from the time of enrollment through Week 12. There were 6 AEs related to the implantation procedure (**Table 2**), and included 1 Horner's Syndrome, which resolved without permanent clinically significant sequelae prior to end of study, and 1 separate incident of postoperative left vocal cord paralysis. Vocal cord paralysis was ongoing at the time of study exit, however it resolved during participation in the long-term extension study without permanent clinically significant sequelae (Genovese 2020).

Table 2: SPM-008 Treatment Emergent AEs Related to the Implantation Procedure

	Stage 1 Open-Label	Stage 2 RCT		
SYSTEM ORGAN CLASS **Preferred Term**	QD (N = 3)	QD (N = 3)	QID (N = 4)	Sham (N = 4)
Subjects with events, n (%)	1 (33.3)	1 (33.3)	2 (50.0)	1 (25.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (33.3)	1 (25.0)	0
Post procedural inflammation	0	1 (33.3)	0	0
Procedural pain	0	0	1 (25.0)	0
NERVOUS SYSTEM DISORDERS	0	0	1 (25.0)	1 (25.0)
Horner's syndrome	0	0	0	1 (25.0)
Vocal cord paralysis	0	0	1 (25.0)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (66.7)	0	0	0
Dermatitis contact	1 (33.3)	0	0	0
Pruritus	1 (33.3)	0	0	0

In conclusion, the pilot study results indicate that the SetPoint System was safe and well-tolerated in this group of RA patients. There were no device-related AEs, and surgical procedure-related AEs resolved without clinically significant sequelae. Several secondary and exploratory efficacy endpoints demonstrated meaningful clinical responses.

All 14 SPM-008 subjects elected to enroll in SPM-011, a long-term extension study with 36-month follow-up. In SPM-011, the subjects who received active stimulation in the base study SPM-008 remained in the same therapy group. The subjects from the QD sham stimulation were randomized at Day 0 in a 1:1 ratio to 1 min QD or 1 min QID dosing. Two (2) subjects were randomized to QD and 2 to QID. Just as in SPM-008, electric current pulses were 250 μs duration at 10 Hz with an output current between 0.25–2.5 mA, which was increased up to the highest tolerated amperage (up to 2.5 mA) on a weekly basis from Day 0 to Week 5. In SPM-011, subjects continued a background therapy of conventional synthetic DMARDs and had the option to add a biologic or targeted synthetic DMARD to the study therapy. As of the 24 Month interim update, 8 of the 11 subjects still enrolled have added a biologic or targeted synthetic DMARD to their treatment. Two device-related AEs have been reported in SPM-011 to date. These occurred in the same subject and were described as sore throat and tenderness near implant site with mild and moderate severity, respectively. Both events resolved without sequelae upon reducing the stimulation strength. In conclusion, VNS stimulation using the SetPoint System for up to 24 months was well tolerated and resulted in stabilization of RA disease activity in most subjects.

8 STUDY OBJECTIVE AND ENDPOINTS

The overall objective of this study is to assess the safety and efficacy of the SetPoint System for the treatment of adult patients with active, moderate to severe RA who have had an inadequate response or intolerance to biologic or targeted synthetic DMARDs.

The study specific objectives and endpoints are defined in **Table 3**.

Table 3: Study Objectives and Endpoints

Objective	Endpoint	Justification of Endpoint
Primary		
To assess the efficacy of the SetPoint System	ACR20 response at Week 12 from baseline on the day of informed consent	The ACR20 response is the most commonly used, RA-specific, clinically relevant, valid and reliable measure of therapeutic effect and clinical benefit of the investigational treatment on signs, symptoms and physical functions.
Secondary		
To further assess the efficacy of the SetPoint System in terms of clinically meaningful benefits	Key secondary efficacy endpoints adjusted for multiplicity: • ACR20 response at Week 12 from Day 0 • DAS28-CRP good/moderate EULAR response at Week 12 • DAS28-CRP response (MCID -1.2) at Week 12 • HAQ-DI response (MCID -0.22) at Week 12	These are RA-specific, clinically relevant, valid and reliable measures of therapeutic effect of the investigational treatment on signs, symptoms and physical functions.
Exploratory		
To provide further information on the therapeutic effect of the SetPoint System	• Exploratory endpoints include, but are not limited to: • ACR20 response at Week 24, 48, 96, 144 and 192 • ACR50/70 response at Week 12, 24, 48, 96, 144 and 192 • 20/50/70 response for ACR components (TJC28, SJC28, Subject Pain, SGA, HAQ-DI, EGA, hsCRP) based on change from baseline to Week 12, 24, 48, 96, 144 and 192 • DAS28-CRP score change from baseline, LDA/remission at Week 12, 24, 48, 96, 144 and 192 • DAS28-CRP response (MCID, good/moderate EULAR) at Week 24, 48, 96, 144 and 192 • CDAI score change from baseline, LDA/remission, response (MCID) at Week 12, 24, 48, 95, 144 and 192 • EQ-5D-5L score change from baseline, response at Week 12, 24, 48, 96, 144 and 192 • SF-36/PCS/MCS score change from	These are clinically relevant, and validated measures of the therapeutic effect on composite measures, patient-reported outcomes, inflammatory biomarkers and structural progression of disease.

	baseline to Week 12, 24, 48, 96, 144 and 192 • RAMRIS bone erosion, osteitis, synovitis, and CARLOS score change from baseline to Week 12 and 24 • RAMRIS bone erosion progression (> 0.5) rate from baseline to Week 12 and 24 • Change in plasma biomarker concentrations (e.g., IL-6, SAA, MMP3)	
Safety		
To evaluate the safety of the SetPoint System	Incidence of AEs and SAEs from informed consent to Week 264 Incidence of device malfunctions from Implant Procedure to Week 264	The incidence of treatment emergent AEs and SAEs that are more common in the treatment group compared to control is a standard measure of the safety. The incidence of device malfunction informs about the device reliability.

9 STUDY DESIGN

9.1 Overall Design

This is an operationally seamless, 2-stage randomized, sham-controlled, double-blind, multicenter pivotal study enrolling at least 240 and up to 250 randomized subjects at up to 45 study centers across the U.S. Enrollment will be conducted in 2 consecutive stages:

- **Stage 1** with approximately 60 randomized subjects at up to 25 study centers; and
- **Stage 2** with approximately 190 randomized subjects at up to 45 study centers, including those from Stage 1.

There will be a pause in enrollment for approximately 6 months after enrolling the last subject into Stage 1 to allow completion of Week 12 for all Stage 1 subjects and readout of comparative data (see Section **17.3**). During the pause in enrollment, Stage 1 subjects will continue to be followed per protocol.

Following primary endpoint assessment at Week 12, there will be a one-way crossover of control subjects to active stimulation and open-label follow-up with all subjects (treatment and control) receiving active stimulation through Week 264 for long-term safety. The initial, 12-week follow-up period will support an application for PMA. Additional follow-up will evaluate long-term safety. Blinding will be maintained until all subjects have completed Week 12 assessments and the study dataset for primary analysis has been locked. A maximum of 20 subjects may be enrolled at a single study center. A schematic of the overall study design is provided in **Figure 12**:

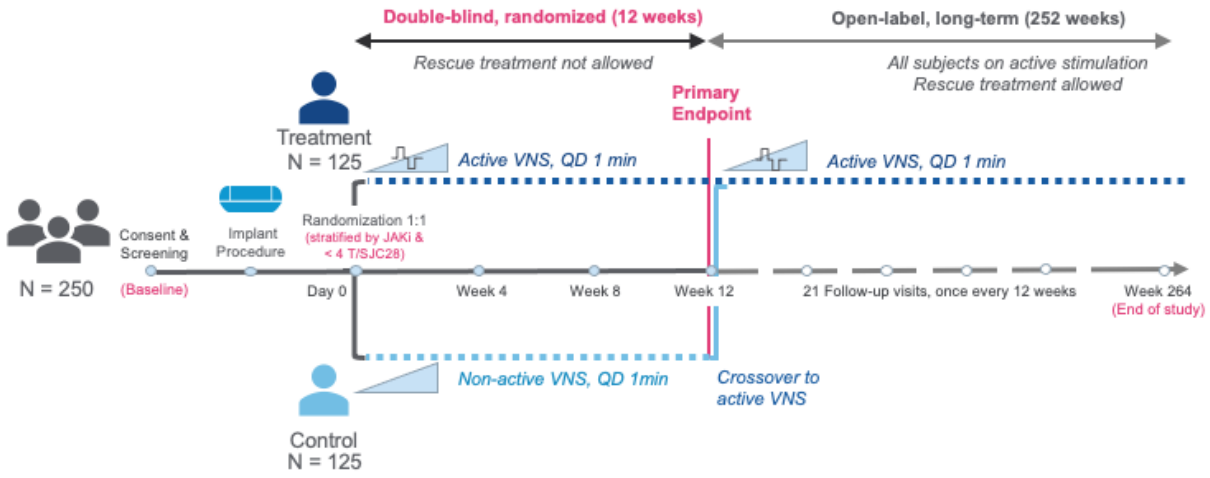


Figure 12: SPM-020 Study Schematic

9.2 Rationale for Study Design

The overall study design is well established to assess the efficacy of a novel treatment in subjects with active moderate to severe RA after failing prior biologic and/or targeted synthetic DMARD therapy and ongoing use of conventional synthetic DMARD.

A key feature of the study is an interim analysis after Stage 1 to assess the initial treatment response, with a stopping rule for the trial if there is lack of efficacy. The Stage 1, 12-week data will be submitted to the DMC and FDA before moving to Stage 2. If the stopping rule is not met, there will be a seamless transition to Stage 2 after receiving DMC and FDA's feedback to continue. This operationally seamless design allows both stages to be conducted under the same study protocol, Institutional Review Board (IRB) approvals, CTA and use of a single database, thereby increasing efficiency.

A control group receiving non-active (sham) stimulation through Week 12 (primary endpoint) is included to measure the absolute effect of active VNS using the SetPoint System, allowing a robust determination of its clinical efficacy and safety profile. Following primary endpoint assessments at Week 12, there will be a one-way crossover of control subjects to active stimulation and open-label follow-up with all subjects (treatment and control) receiving active stimulation for 1 min once per day through Week 264 in order to assess long-term safety. All subjects must continue stable background therapy with at least 1 conventional synthetic DMARD started at least 12 weeks prior to informed consent to ensure that approved RA treatment is not withheld from control subjects and to ensure that all subjects remain blinded. In addition, the investigator can withdraw a subject from the study at any time as clinically indicated. Additional RA treatment may be provided at the discretion of the clinical investigator and subject at any time after completion of assessments at Week 12.

Follow-up visits are scheduled at least once every 12 weeks to ensure continuous oversight of the subject's safety, collect laboratory samples to detect any abnormalities and determine RA disease activity. This timing is aligned with most drug studies and routine standard of care.

10 STUDY POPULATION

The study population will consist of adults (22-75 years of age) with active, moderate to severe RA who have had an inadequate response, loss of response or intolerance to 1 or more biologic or targeted synthetic DMARDs, including JAKi.

Subjects with inadequate response or loss of response to JAKi will be limited to 6 subjects.

10.1 Inclusion Criteria

Subjects eligible for enrollment in the study must meet *all* of the following inclusion criteria:

1. Male or female and 22-75 years of age, inclusive, at the time of informed consent
2. Provided written informed consent by signing a form approved by the reviewing IRB
3. Have active, moderate to severe RA, defined as at least 4/28 tender joints and 4/28 swollen joints
4. Demonstrated an inadequate response, loss of response, or intolerance to 1 or more approved for RA biologic or targeted synthetic DMARDs, including JAKi
5. Receiving treatment with at least 1 conventional synthetic DMARD for at least 12 weeks prior and on a continuous, non-changing dose 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 is acceptable, except during the 4 weeks preceding informed consent. Permitted conventional synthetic DMARDs and their approved for RA dosage are:
    a. Hydroxychloroquine (200-400 mg/day)
    b. Leflunomide (10-20 mg/day)
    c. Methotrexate (10-25 mg/week)
    d. Sulfasalazine (1,000-3,000 mg/day)

    Higher stable doses are allowed if indicated by treating physician. Lower stable doses are allowed if dose limiting toxicity precludes using higher doses. Combinations are allowed provided all drugs comprising the combination meet stability requirements.
6. Willing and able to comply with protocol requirements

10.2 Exclusion Criteria

Subjects eligible for enrollment in the study must meet *none* of the following exclusion criteria:

1. Have taken biologic or targeted synthetic DMARDs within the minimum required number of washout days prior to Implant Procedure (see **Appendix A**)
2. Demonstrated an inadequate response or loss of response to JAKi, once 6 subjects meeting this criterion have been enrolled.
3. Have received an intra-articular corticosteroid injection within 30 days of Implant Procedure
4. Are currently receiving glucocorticoids at doses greater than 10 mg QD of prednisone (or equivalent) or have been receiving an unstable dosing regimen within 14 days of informed consent
5. Have started treatment with NSAIDs or have been receiving an unstable dosing regimen of NSAIDs within 14 days of informed consent. Over-the-counter use of NSAIDs is permissible (see Section 14.3)
6. Regular use of or dependency on nicotine products within the past 2 years, including but not limited to cigarettes or other nicotine-containing products such as cigars, pipe tobacco, chewing tobacco, patches, gums, lozenges, or electronic cigarettes. Subject does not agree to abstain from using nicotine-containing products throughout study participation.
7. Woman who is either pregnant or breast feeding
8. Woman of childbearing potential who does not agree to use an effective method of contraception. If a woman becomes or decides she wants to become pregnant, the implant must be decommissioned and the subject followed for safety, per standard of care.
9. Untreated or poorly controlled psychiatric illness or history of substance abuse
10. Active infection requiring treatment with antibiotics or corticosteroids at Screening, unless cleared before Implant Procedure
11. Significant immunodeficiency due to underlying illness (e.g., active, untreated HBV/HCV and HIV positive)
12. History of CVA or transient ischemic attack, or diagnosis of cerebrovascular fibromuscular dysplasia
13. Clinically significant cardiovascular disease, including cardiomyopathy with ejection fraction < 40%, myocardial infarction, unstable angina, or diagnosis of congestive heart failure (NYHA Class III or IV) in the preceding 12 months. Subjects with current, clinically significant cardiovascular disease must obtain clearance from a cardiologist prior to the implant procedure
14. Neurological syndromes including multiple sclerosis, Alzheimer's disease, or Parkinson's disease
15. Fibromyalgia that may confound outcome measures such as tender joint count, evaluator's global assessment, subject's global assessment, subject's pain, HAQ-DI, SF-36, or EQ-5D-5L

16. Known clinically significant cerebrovascular atherosclerotic disease including contralateral carotid artery disease (non-implanted side)
17. History of or pre-surgical X-ray that shows cervical spine disorder or instability that, in the investigator's opinion, would preclude safe endotracheal anesthesia or could be exacerbated by the implant procedure
18. Estimated glomerular filtration rate (eGFR) less than or equal to 50 mL/min/1.73 m2 at Screening. eGFR eligibility must be confirmed prior to Screening hand MRI
19. History of left or right carotid surgery (e.g., carotid endarterectomy or stent)
20. History of unilateral or bilateral vagotomy
21. Partial or complete splenectomy
22. Recurrent vasovagal syncope episodes
23. Clinically significant cardiac rhythm disturbances, or ECG findings of atrioventricular block exceeding first degree, or cardiac conduction pathway abnormalities other than isolated right bundle branch block and/or isolated left anterior fascicle block on Screening ECG
24. Cancer within last 3 years, except fully resected basal or squamous skin cancer, fully resected cervical carcinoma in situ, or fully treated mammary ductal carcinoma in situ that has been in clinical remission for at least 3 years
25. Clinically significant esophageal dysfunction such as dysphagia, odynophagia, or esophagitis
26. History of or current, clinically significant vocal cord dysfunction, vocal cord polyps, or thyroid nodules.
27. Active and uncontrolled peptic ulcer disease
28. Implanted active medical devices (e.g., cardiac pacemakers, automatic implantable cardioverter-defibrillators, drug pumps), or likely need for implantation of such devices within 6 months
29. Uncontrolled asthma, chronic obstructive pulmonary disease, sleep apnea, or any other pulmonary disease such as interstitial lung disease causing clinically significant dyspnea
30. Limited life expectancy due to terminal disease
31. Hypersensitivity/allergy to MRI contrast agents and/or unable to perform MRI (e.g., claustrophobia)
32. Unable to use or wear Energizer
33. Requires treatment by any of the prohibited interventions (see Section 14.4)
34. Currently participating in another clinical research study with an investigational drug or medical device
35. Have taken an investigational drug for RA within the defined time period prior to Implant Procedure:

a. Have taken an investigational drug consisting of biologic agents within 30 days prior to Implant Procedure
b. Have taken an investigational drug consisting of small molecules within 30 days or 5 times the pharmacokinetic half-life, whichever is longer, of Implant Procedure

36. Uncontrolled hypertension
37. Uncontrolled diabetes mellitus
38. Any comorbidity or current status of subject's physiological fitness that in the surgeon's or anesthesiologist's opinion represents safety concerns that make the subject medically unfit for the implant procedure or may prevent proper placement of MicroRegulator and POD
39. A positive COVID-19 test between informed consent and Implant Procedure
40. Works or resides in an environment where radio frequency (RF) exposure is higher than levels deemed safe for normal daily activity by the general public (e.g., near radio or television broadcasting antennas, radar systems, industrial heaters and sealers)
41. Any condition that, in the investigator's opinion, may preclude completion of screening, implant procedure, and post-surgical clearance over the course of 6-7 weeks or follow up assessments over the course of 192 weeks (e.g., a medical condition that may increase the risk associated with study participation or may interfere with interpretation of study results, inability to adhere to the visit schedule, or poor compliance with treatment regimen)
42. History of thyroid surgery, parathyroid surgery, or other previous neck surgery that, in the opinion of the Co-PI Surgeon, puts the subject at increased risk of surgical complications
43. BMI at screening ≥ 35 kg/m^2
44. Use of high potency opioids. Examples include (but are not limited to): morphine, hydromorphone, methadone (Dolophine), meperidine (Demerol), oxycodone (OxyContin, Percocet), oxymorphone, fentanyl (Sublimaze, Duragesic), levorphanol (Levo Dromoran), and buprenorphine (Subutex, Suboxone)

Note: Use of high potency opioids is not permitted during participation except for analgesic care related to an AE.

45. Inflammatory joint disease other than RA (including but not limited to gout, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis, reactive arthritis, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis. Current diagnosis of secondary Sjogren's Syndrome is permitted

10.3 Subject Status

Subjects will be classified as follows depending on their current status:

- *Consented.* After signing an IRB-approved informed consent form
- *Screen failure*. Subject not meeting all inclusion or meeting any exclusion criteria
- *Enrolled*. Subject meeting all inclusion and none of exclusion criteria in whom the implant procedure is attempted
- *Implanted.* Subject in whom the implant procedure is successfully completed
- *Randomized*. After being randomly assigned to either treatment or control group
- *Withdrawn*. Meeting one of the withdrawal conditions listed in Section **10.4**; or
- *Completed study*. After completing the study-required assessments at Week 264.

10.4 Subject Withdrawal

Enrolled subjects may be withdrawn for any of the following reasons:

- Subject death
- Concomitant disease or any pre-existing disease or condition that precludes subject's participation
- Subject voluntarily chooses not to participate further in the study
- Subject's non-compliance with study procedures
- Lost to follow-up, if a subject has missed a study visit, and 3 documented attempts to contact the subject have been unsuccessful. A subject who misses a study visit should be contacted by site personnel to determine the reason for the missed visit, which should be documented in the subject's study records. A subject who misses a study visit but attends a subsequent visit will no longer be considered lost to follow-up
- In the clinical investigator's opinion, a significant safety concern arises that requires subject discontinuation
- In the clinical investigator's opinion, it is not in the best interest of the subject to continue study participation
- In the study sponsor's or IRB's opinion, it is not in the best interest of subject to continue the study; or
- Study is terminated.

Clinical investigators should follow withdrawn subjects with ongoing AEs until resolution according to standard of care. Data collected up to the point of subject withdrawal or termination will be maintained in the study database and included in analyses as appropriate.

If, upon withdrawal, a subject wants or needs to have their implant permanently turned off and left in place, the implant will be decommissioned at the subject's last scheduled visit, or an unscheduled visit, if necessary. Implant decommissioning is described in Section **11.9**.

If, upon withdrawal, a subject wants or needs to have their implant removed, an explant procedure will be scheduled according to protocol Section **11.10**.

All enrolled subjects, including those withdrawn, will be accounted for and documented.

11 SUBJECT TREATMENT AND STUDY PROCEDURES

11.1 Pre-screening

During the pre-screening phase, clinical investigators or designees will perform an initial evaluation of potential candidates for study eligibility by reviewing their medical records to identify previously performed diagnostic measures, medical history, and labs in an effort to rule out subjects most likely ineligible for the study. Patients will be pre-screened as close to the date of consent and screening as is practicable. This will be included in the site training for the study. A log should be maintained to record limited details of those who were pre-screened, tracking the outcome of the screening (e.g., ineligible, potentially eligible but declined further study involvement, potentially eligible and attended a screening visit).

11.2 Informed Consent and Screening

11.2.1 Informed consent

If the patient appears to be a potential candidate for the study based upon existing information, a written informed consent will be obtained. Informed consent must be obtained prior to initiation of any clinical procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from medication. Patients who have completed or are in process of washout unrelated to this study may be considered for the study. When washout is done solely in anticipation of or in preparation for the research, it is part of the research and must be done after obtaining written consent.

Clinical investigators or designees will approach the patient to obtain a written informed consent. The background of the proposed study, the implant procedure, the follow-up schedule and all potential risks and benefits will be carefully explained to each patient. The clinical investigator or designee obtaining informed consent shall:

- Avoid any coercion of or undue influence of patients to participate,
- Not waive or appear to waive patient's legal rights,
- Use language that is non-technical and understandable to the patient, and
- Provide ample time for the patient to consider participation.

Each patient must sign and date the ICF approved by an appropriate IRB during an in-office visit. The original signed ICF will be placed in the study file, and a copy will be given to the subject.

Subjects will be re-consented in situations where changes were made to the study protocol or new information about the risks, possible benefits or alternative treatments have been identified. The sponsor and IRB will notify clinical investigators in the event re-consent is necessary. In this case, subjects must sign and date the amended ICF during their next in-office visit. The original will be placed in the study file, and a copy will be given to the subject.

11.2.2 Screening and baseline assessments

During the same in-office visit that written informed consent is obtained, each subject will be assigned a unique identifying code and undergo the following screening assessments to confirm their initial eligibility and obtain baseline values for RA disease activity assessments from which the primary and the key secondary efficacy endpoints will be assessed:

- Physical examination, including vital signs, height and weight

Note: If a subject has an active infection that does not clear before Implant Procedure, the subject is considered as a screen failure. The subject can be consented and screened following treatment and full recovery.

- Prior and current RA medications with detailed record of use of biologic, conventional and targeted synthetic DMARDs
- Medical history
- Female subjects of childbearing potential must confirm their nursing status, undergo pregnancy test, and confirm their birth control method(s) (see Section **12.1**)
- RA disease activity assessments (see Section **12.2**)
- Determining the need for washout from biologic or targeted synthetic DMARDs prior to Implant Procedure, depending on subject's current usage:
    - *Subjects in post-washout, requiring no further washout*. Subjects who stopped taking all biologic and targeted synthetic DMARDs for a period exceeding the required minimum washout period prior to Implant Procedure (see **Appendix A**) do not require further washout to qualify for the study.
    - *Subjects during washout, requiring completion of washout.* Subjects who stopped taking any biologic and targeted synthetic DMARDs within less than the required minimum washout period prior to Implant Procedure (see **Appendix A**) must complete washout during the screening period, prior to Implant Procedure to qualify for the study.
    - *Subjects in pre-washout, requiring washout.* Subjects who are currently taking any biologic and/or targeted synthetic DMARDs must stop taking them for the required minimum washout period during the screening period, prior to Implant Procedure (see **Appendix A**) to qualify for the study.

Note: If the required minimum washout period following informed consent exceeds 30 days for a given subject, this subject shall be considered screen failure without the possibility of reconsenting. This is because washout needs to be completed before Implant Procedure, which takes place within 30 days from the informed consent date.

- Energizer fit test
- Eligibility evaluation

The remaining screening assessments can be completed on the day of informed consent or shortly after, depending on scheduling abilities:

- Concomitant medications
- SF-36 and EQ-5D-5L questionnaires
- Blood collection for RF, ACPA, eGFR, CBC and biomarkers (see Section **12.3**)

Note: eGFR must be confirmed prior to screening hand MRI

- Hand MRI (see Section **12.4**)
- Reporting of any AEs

Pre-surgical clearance must be completed by the Co-PI Surgeon prior to the scheduled implant procedure and entails:

- Review of the screening data collected by the rheumatologist investigator
- 12-lead ECG and any additional tests required for surgical or anesthesia clearance per hospital's standard of care
- Standard cervical spine X-ray, including anterior-posterior, lateral full flexion and extension, and odontoid views to ensure there are no degenerative or inflammatory changes observed in the cervical spine that would predict significant risk for atlanto-axial subluxation during neck extension required for endotracheal intubation prior to implantation (Krause and Matteson 2014). Cervical spine disorders or instability that would preclude safe endotracheal anesthesia will render the subject ineligible. The radiology report shall be filed with the subject's source documentation.
- An assessment of eligibility based on criteria associated with comorbidities or current status of physical fitness that would make the subject medically unfit for the implant procedure.

Based on all screening assessments, Co-PI Rheumatologist conducts a final eligibility evaluation:

- A subject must meet all the inclusion criteria and none of the exclusion criteria to be eligible. A subject not meeting all inclusion criteria or meeting any exclusion criterion will be classified as a screen failure and exited from the study. The reason(s) for screen failure will be documented.

11.3 Enrollment and Implant Procedure

Subjects meeting final eligibility criteria and in whom the implant procedure is attempted are considered enrolled. The implant procedure shall occur within 30 days from informed consent. The implant procedure is an outpatient procedure taking place in an operating room under general anesthesia. The implant (MicroRegulator) and POD will be placed on the left cervical vagus nerve within the carotid sheath by surgeons trained and experienced in procedures involving implantation of VNS devices. The implant procedure must be performed according to SetPoint System Instructions for Use Surgeon Manual. All surgeons performing the implant procedure must have documented training prior to performing the first case. Upon completing the implant procedure, any AEs, device deficiencies and changes in concomitant medications will be recorded.

The pregnancy testing for female subjects of childbearing potential must be completed before initiation of the implant procedure (see Section **12.1**).

11.4 Post-Surgical Clearance

Subjects will undergo the following assessments within 14-21 days after Implant Procedure and prior to Day 0:

- Pregnancy test for female subjects with childbearing potential and confirmation of birth control method (see Section **12.1**)
- Surgical clearance, which includes:
  - Post-operative surgical evaluation of wound healing by the Co-PI Surgeon or designee at the surgical site, with special attention to wound infections
  - Final surgical clearance with an approval to initiate study treatment
- Reporting of any AEs, device deficiencies and change in concomitant medications

11.5 Day 0 Assessments, Randomization, and Initiation of Stimulation

11.5.1 Day 0 assessments

Subjects approved to initiate study treatment will undergo the following assessments within 14-21 days after Implant Procedure and before randomization:

- Collection of vital signs
- Pregnancy test for female subjects of childbearing potential and confirmation of birth control method (see Section **12.1**)
- RA disease activity assessments (see Section **12.2**)
- SF-36 and EQ-5D-5L questionnaires

- Blood collection for CBC and inflammatory biomarkers (see Section **12.3**)
- Reporting of any AEs, device deficiencies and change in concomitant medications.

11.5.2 Randomization

Upon completion of all Day 0 assessments, subjects will be randomly assigned in a 1:1 ratio to either treatment or control group using an interactive response technology (IRT) system. Subjects assigned to the treatment group will receive active stimulation for 1 min once per day, and those assigned to the control group will receive sham (non-active) stimulation for 1 min once per day. Subjects and study staff will be kept blinded (see Section **18.3**).

For subjects assigned to the control group, their MicroRegulator will be registered to a prescription rule to deliver a sham stimulation, regardless of the setting assigned. The registration is performed by unblinded technicians at SetPoint Medical who have exclusive access to the subject's treatment assignment. The prescription rule is written in the SetPoint Medical cloud and is received by the site's Prescription Pad when connected to Wi-Fi and then applied to MicroRegulator via Energizer. The prescription rule is not visible to the site personnel to ensure they remain blinded to treatment assignment.

11.5.3 Initiation of stimulation

After randomization, all subjects (treatment and control) will undergo device check, dose titration and training on the use of Energizer. The device check and dose titration must be performed by a study staff member at the rheumatology site who has been delegated as the site's device programmer and completed the required programming training. Both delegation and training must be documented in the appropriate forms.

11.5.4 Device check and dose titration/adjustment

Device check

The research coordinator or designee delegated to perform device programming will first perform a device check and then dose titration while subjects are wearing their Energizer. The device check entails connecting Prescription Pad to the site's WiFi and establishing the Bluetooth connection between Prescription Pad and the subject's Energizer. Once Prescription Pad is connected to Energizer, and Energizer is connected to MicroRegulator, Prescription Pad will display the following information:

- Current prescription settings (i.e., strength of stimulation)
- Total number of doses delivered at current setting
- Number of doses missed
- MicroRegulator battery level
- MicroRegulator impedance

*Note: If a charge level of less than 75% is observed, the subject will be counseled on the importance of charging their implant on a weekly basis. Failure to charge the MicroRegulator for an extended period may result in a complete discharge of its battery. Once fully discharged, the battery cannot be recharged, and automatic delivery of stimulation will no longer occur. In this case, the MicroRegulator must be decommissioned (permanently turned off) and the subject must return all external equipment (Energizer and Wireless Charger) (see Section **11.9**).*

Dose titration

Dose titration entails an iterative procedure during which short test stimulations will be delivered and assessed by subject for tolerability. If tolerated, the stimulation strength will be incremented and assessed again. This will be repeated to the maximum level tolerated or to the maximum allowable current level specified for the visit, whichever comes first. Once the desired stimulation strength is determined or achieved, the subject's MicroRegulator will be set to deliver stimulation at that dose for 1 minute per day. The device programmer will follow the same schedule and procedure for all subjects (treatment and control). Subjects, regardless of treatment assignment, should not be told or shown what their stimulation strength is set to.

The titration visits occur at timepoints specified in Section **6**. Titration visits will be short and consist of a device check and dose titration, as described above. No study required RA assessments will be performed during those visits. All AEs, device deficiencies and changes in concomitant medications will be recorded. Female subjects with childbearing potential will undergo a pregnancy test and confirmation of birth control method per Section **12.1**.

Dose adjustment

If there is a need to change the stimulation strength, a dose adjustment may be performed. The reason for dose adjustment must be documented. Reasons include an AE such as subject side effect (see Section **16.2**). The process for adjusting the stimulation strength is similar to that for dose titration and consists of short test stimulations that are assessed by subject for tolerability. If tolerated, the stimulation strength will be incremented and assessed again. This will be repeated to the maximum level tolerated. Once the desired stimulation strength is determined or achieved, the subject's MicroRegulator will be set to deliver stimulation at that dose for 1 minute per day.

11.6 Follow-up

The follow-up period begins immediately post-randomization and initiation of stimulation. Each subject will return for 6 follow-up visits between Day 0 and Week 12, and 24 follow-up visits in the open-label, long-term follow-up period, starting after Week 12 assessments and continuing through Week 264 (end of study). Visits must occur within specified windows from Day 0 as detailed in Schedule of Assessments (see Section **6**).

The protocol-required follow-up assessments are described in the following sections.

11.6.1 Follow-up through Week 12

The protocol-required follow-up assessments at Week 4, 8 and 12 include the following and should be performed in the order specified prior to the device check and any dose adjustment:

- Subject's, Joint Evaluator's and Co-PI Rheumatologist blinding assessment (Week 4 and 12)
- Collection of vital signs (Week 12)
- 12-lead ECG (Week 12)
- Pregnancy test for female subjects with childbearing potential and confirmation of birth control method (see Section **12.1**)
- RA disease activity assessments (see Section **12.2**)
- SF-36 and EQ-5D-5L questionnaires
- Blood collection for CBC and inflammatory biomarkers (see Section **12.3**)
- Reporting of any AEs, device deficiencies and change in concomitant medications
- Suspending therapy before the hand MRI (Week 12; see Section **11.8**)
- Hand MRI (Week 12; see Section **12.4**)
- Review of clinical outcomes and discussion of treatment options for continuation in the long-term follow-up period of the study (after completing assessments at Week 12). The Co-PI Rheumatologist will review with the subject their clinical outcomes and determine which option is in the subject's best interest. The Co-PI Rheumatologist and the subject are blinded to initial treatment assignment in making this decision. The option chosen will be recorded on the follow-up visit CRF and entered into EDC. Options include:
  - Receive active stimulation
  - Receive additional RA treatment with active stimulation (see Section **14.5**)
  - Receive additional RA treatment without active stimulation (i.e., stimulation is suspended, see Section **11.8**) with a possibility to receive active stimulation at a later time
  - Permanently turn off (decommission) the study implant (see Section 11.9)
  - Undergo an explant procedure to surgically remove the implant (see Section **11.10**)
- Re-registration of Microregulator following MRI at Week 12. Cross-over of the control group to active stimulation by updating the prescription rule to deliver active stimulation. The prescription rule for treatment subjects will remain the same, delivering active stimulation. Re-registration will be performed by unblinded technicians at SetPoint Medical. The blind for all study roles that are blinded will be maintained (see Section **18.3**).
- Device check and dose titration following MicroRegulator re-registration at Week 12, depending on the option chosen for long-term follow-up.

11.6.2 Open-label, long-term follow-up through Week 264

Protocol-required follow-up assessments at Week 24 through Week 264 are detailed below and in Schedule of Assessments (see Section **6**) and should be performed in the order specified prior to the device check and any dose adjustment:

- Collection of vital signs
- 12-lead ECG (Week 24, 48, 96, 144, 192)
- Pregnancy test for female subjects with childbearing potential and confirmation of birth control method (see Section **12.1**)
- RA disease activity assessments (see Section **12.2**)
- SF-36 and EQ-5D-5L questionnaires (Week 24, 48, 96, 144, 192)
- Satisfaction Questionnaire (Week 24)
- Blood collection for CBC (see Section **12.3**)
- Blood collection for inflammatory biomarkers (Week 24) (see Section **12.3**)
- Reporting of any AEs, device deficiencies and change in concomitant medications, including the need, timing and type of additional RA treatment
- Suspending therapy before the hand MRI and resuming therapy afterwards (Week 24; see Section **11.8**)
- Hand MRI (Week 24; see Section 12.4)

At Week 264, once all assessments are completed, every subject's MicroRegulator must be decommissioned (see Section **11.9**).

11.7 Unscheduled Visits

Subjects may come for additional unscheduled office visits if necessary. Circumstances that may warrant additional visits include but are not limited to:

- RA-related AEs requiring medical evaluation
- Device deficiency evaluation; and/or
- Device dose adjustment, suspending stimulation, resuming stimulation or implant decommissioning.

Unscheduled visits are related to the study and not standard of care. Prescription refill visits are not considered unscheduled visits. Information gathered during an Unscheduled visit must be recorded and entered into the study database on the appropriate CRF.

11.8 Suspending and Resuming Stimulation

Stimulation must be suspended before an MRI, prior to an elective surgical procedure, or if there is a concern of subject's safety.

Additionally, stimulation may be suspended at any time after completion of Week 12 assessments at the discretion of the clinical investigator and the subject. The clinical investigator and subject may decide to suspend stimulation in the event the subject experiences worsening of RA symptoms or if the subject does not experience adequate clinical improvement and continuation of stimulation is deemed not in the best interest of the subject (e.g., subject experiences AE that is definitely or probably related to stimulation). RA disease activity is assessed and documented at all follow-up visits. Results from these assessments may be used to guide decision-making.

MicroRegulator should be fully charged prior to suspending stimulation. Stimulation from MicroRegulator can be suspended by Prescription Pad as detailed under "Suspending Therapy" section of the SetPoint System IFU Prescriber Manual. Pink visual indicator on Energizer confirms therapy suspension. Stimulation will no longer be delivered until therapy is resumed. Subjects should continue to follow the regular visit schedule, adhere to all study procedures and be monitored for safety while therapy is suspended.

If the clinical investigator and subject decide to resume stimulation (examples include, but are not limited to, following resolution of AE, after MRI, after elective procedure), stimulation from MicroRegulator can be resumed by Prescription Pad as detailed under "Resuming Therapy" section of the SetPoint System IFU Prescriber Manual. Green or orange visual indictor on Energizer confirms that therapy has been resumed.

11.9 Implant Decommissioning

Implant battery charge level will be monitored by the designated research coordinator at every follow-up visit. If a charge level of less than 75% is observed, the subject will be counseled on the importance of charging their implant on a weekly basis and be reminded that their implant will be decommissioned in the event the subject does not comply. Once fully discharged, the battery cannot be recharged, and automatic delivery of stimulation will no longer occur. In this case, the MicroRegulator must be decommissioned (permanently turned off) and the subject must return all external equipment (Energizer and Wireless Charger). Contact SetPoint Medical to request placement of the MicroRegulator in decommission mode. If a subject wants or needs to have their implant permanently turned off and left in place at the end of the study or earlier, the implant will be decommissioned in accordance with the SetPoint System Instructions for Use Prescriber Manual. The subject would be required to return their Energizer and visit the site at least 24 hours following the initiation of decommissioning, to ensure that the decommissioning process occurred as expected.

Subjects that have their implant decommissioned prior to Week 264 and remain in the study should continue to follow the regular visit schedule, adhere to all study procedures and be

monitored for safety. Subjects choosing to end participation after implant decommissioning will be asked to contact the clinical investigator in the event they experience any safety issue related to the investigational implant.

If a device failure precludes decommissioning, the subject will be followed for safety for a period of 10 months, at which point the internal battery would be fully depleted. If the 10-month period has not elapsed at the point the subject exits the study, investigator agrees to follow subject under their standard of care. In this case, follow-up will constitute documented contact with the subject once every 2 months, along with documentation of any reported AEs. Subjects will be informed about the risks associated with attempting to recharge a device that has a completely depleted battery.

11.10 Explant Procedure

If a subject wants or needs to have their implant removed at the end of the study or earlier, this must be communicated to the study sponsor prior to scheduling or performing the explant procedure. Before the explant procedure, MicroRegulator stimulation must be suspended (see Section **11.8**). The surgical investigator will perform pre-surgical clearance testing per standard of care. The surgical investigator will remove the implant according to the explant procedure protocol outlined in SetPoint System Instructions for Use Surgeon Manual. In the event an implant cannot be explanted, it will be decommissioned. In the unlikely event that a failed implant cannot be explanted, and the nature of device failure precludes decommissioning, the subjects will be followed for safety for a period of 10 months, at which point the internal battery would be fully depleted. (see Section **11.9**).

The explanted MicroRegulator and POD shall be returned to SetPoint Medical according to the return shipping instructions provided or disposed according to investigator's institutional procedures for disposal of blood contaminated medical devices. Following the explant procedure, subjects will be evaluated to assess for proper wound healing and post-op recovery per standard of care. Once the subject is cleared post-surgery, the subject will exit the study. Any AE resulting from the explant procedure should be followed to resolution.

11.11 Duration of Study Period

The study duration is approximately 84 months (8 months for enrollment into Stage 1, 6 months for a pause in enrollment after Stage 1, 12 months for enrollment into Stage 2, and approximately 58 months for completion of follow-up).

For a given subject, the maximum study duration is 1,899 days (about 5 years, 3 months):

- 30 days from informed consent to Implant Procedure
- 21 days between Implant Procedure and randomization at Day 0
- 84 days (about 3 months) between initiation of stimulation at Day 0 to Week 12

- 1,764 days (about 4 years, 10.5 months) between Week 12 and Week 264

A timeline of the key study visits is provided in **Figure 13**.

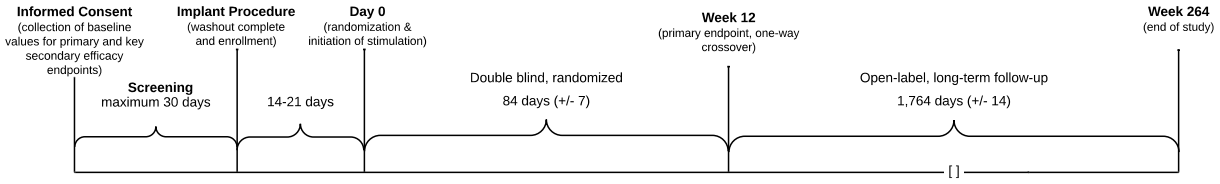


Figure 13: SPM-020 Study Timeline

12 STUDY PROCEDURES

12.1 Pregnancy Test and Birth Control Methods

Female subjects of childbearing potential must undergo a pregnancy test and confirm birth control method on the day of informed consent, before initiation of the implant procedure, and at each follow-up visit in accordance with Schedule of Assessments (see Section **6**). Female subjects that are post-menopausal or who have documented surgical history of hysterectomy or tubal ligation are not considered to be of childbearing potential.

In case of a positive pregnancy test before Implant Procedure, the subject will be considered as a screen failure and will exit the study.

In case of a positive pregnancy test after Implant Procedure, the pregnancy will be reported as an AE, the implant must be decommissioned (see Section **11.9**) and the subject followed for safety, per standard of care. Data collected up to this point will be maintained in the EDC and included in the safety analysis.

Risks associated with use of conventional synthetic DMARDs during pregnancy are identified in the labeling supplied with these drugs and should be reviewed with the subject. Leflunomide and Methotrexate should be stopped immediately in case of a positive pregnancy test, in accordance with the package labeling.

Female subjects of childbearing potential will be required to use acceptable birth control method(s) during the entire duration of the study. Acceptable methods of contraception may include:

- Established use of hormonal contraceptives (e.g., oral, injectables, vaginal ring, intra-uterine device, implant, transdermal patch);
- Non-hormonal IUD
- Double-barrier methods contraceptives (i.e., condom, diaphragm or cervical/vault caps used with spermicide (foam, gel, film, cream or suppository);

- Vasectomized male partner, if the sole partner for the subject;
- Non-sexually active female; or
- Same-sex partner.

12.2 RA Disease Activity Assessments

RA disease activity assessments are listed below and shall be performed in the order indicated:

- HAQ-DI
- SGA
- Subject's pain assessment
- TJC28
- SJC28
- EGA
- hsCRP

Refer to Section 3 for definitions of terms.

12.2.1 HAQ-DI

Subjects will complete the HAQ-DI questionnaire using a paper form.

12.2.2 SGA

Subjects will complete a global assessment of their RA disease activity using a paper form. Subjects must complete their assessments independently from Joint Evaluator's assessment.

12.2.3 Subject's Pain Assessment

Subjects will complete their assessment of the severity of their RA-related pain using a paper form.

12.2.4 TJC28 and SJC28

A total of 28 joints will be scored for presence or absence of tenderness or pain and swelling. All joint assessments will be performed by an independent, blinded Joint Evaluator with appropriate training and experience. Each subject should be assessed by the same Joint Evaluator throughout their participation in the study. The subject's Joint Evaluator *must* be the same at Screening and Week 12. Joints that have been replaced or injected with intra-articular steroids during the study are considered unevaluable.

12.2.5 EGA

After performing joint assessments, the same Joint Evaluator will conduct a global assessment of the subject's RA activity using a paper form. Each subject should be assessed by the same Joint Evaluator throughout their participation in the study. The subject's Joint Evaluator *must* be the same at Screening and Week 12. The Joint Evaluator must complete their assessments without knowledge of SGA.

12.2.6 hsCRP

Blood samples for hsCRP will be collected using sampling kits and shipped at room temperature to a central laboratory for analysis through Week 192 (see Section **12.3**). Serum concentration of hsCRP (mg/L) will be determined by immunoturbidimetric assay. Blood samples for hsCRP will be analyzed locally from Week 204 through Week 264.

12.3 Clinical Laboratory Tests

Blood samples will be collected at the site and sent to a central laboratory (ICON Laboratory Services) through Week 192. Analysis will include the following according to the schedule of assessments (see Section **6**):

- RF
- ACPA
- eGFR
- CBC; and
- Inflammatory biomarkers (e.g., IL-6, SAA, MMP3).

The central laboratory will provide each site with sampling kits, shipping boxes and detailed instructions on blood sample collection, preparation and shipping.

Blood samples collected at Week 204 through Week 264 will be analyzed locally. The following analytes will be tested:

- Complete blood count (CBC), platelet count, differential count

All laboratory reports shall be reviewed by the site investigator and filed in the subject binder. In the event of a clinically significant abnormality, an adverse event shall be reported and labs shall be repeated and monitored at the investigator's discretion until resolved or considered medically stable.

Samples collected for surgical clearance shall be in accordance with the site's standard of care practices and analyzed locally. Testing may include:

- Platelet count, differential count
- Serum sodium, potassium, bicarbonate, chloride, magnesium, calcium, BUN, serum creatinine
- Urinalysis; and
- PT, PTT, INR.

12.4 Hand MRI

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

The MRI images will be acquired before and after intravenous administration of gadolinium-based contrast to maximize sensitivity and specificity for inflammation. Instructions on image acquisition will be provided in a separate manual from the MRI central laboratory. The same hand must be imaged using the same MRI scanner and coil at Screening, Week 12, and Week 24 for a given subject. Only 1.5T and 3.0T whole-body scanners and transmit-receive (Tx/Rx) coils, ideally knee coils, are acceptable for this study. In vitro testing of MicroRegulator and POD indicates that it passes standard testing for safe use in 1.5 T and 3.0 T MRI studies. Safe scanning parameters are provided in the SetPoint Medical Surgeon, Prescriber and Patient Manuals.

The MRI images will be transmitted promptly to the MRI central laboratory for quality check, reading and quantification. If any of the images are rejected for inadequate quality, the subject shall be scheduled for a repeat MRI within 7 days from the first MRI date.

13 STUDY SUPPLIES AND DEVICE ACCOUNTABILITY

The investigational study devices will be provided to each site upon study sponsor collection and approval of all required regulatory documentation. The device will be labeled “CAUTION: Investigational Device. Limited by United States Law to Investigational Use” and must be stored in a secure (locked) area under the appropriate storage conditions. Access should be limited to designated study staff only. Device accountability logs will be provided to the site. It is the site’s responsibility to document the receipt (maintain shipping records), disposition (per subject use), transfer (if applicable) and return of all study devices.

All unused or expired investigational devices must be returned to SetPoint Medical in accordance with its Return Material Authorization procedures. Explanted Microregulator and POD can be returned or disposed according to investigator’s institutional procedures for disposal of blood contaminated medical devices.

14 PRIOR AND CONCOMITANT MEDICATION

14.1 Prior RA Medication

Prior use must start from date of RA diagnosis and include all approved for RA biologic and targeted synthetic DMARDs. At a minimum, the year of start and stop must be recorded. The subject's medical record should substantiate the type, dose and duration of usage, as well as reason for stopping.

14.2 Required Background RA Therapy

Each subject must continue a background therapy with at least 1 conventional synthetic DMARD started at least 12 weeks prior and at a stable dose since at least 4 weeks prior to informed consent and until Week 12. Missing up to 2 doses due to COVID-19 vaccination is acceptable, except during the 4 weeks preceding informed consent.

Permitted conventional synthetic DMARDs and their approved for RA dosage are:

- Hydroxychloroquine (200-400 mg/day)
- Leflunomide (10-20 mg/day)
- Methotrexate (10-25 mg/week)
- Sulfasalazine (1,000-3,000 mg/day)

Higher stable doses are allowed if indicated by treating physician. Lower stable doses are allowed if dose limiting toxicity precludes using higher doses. Combinations of oral conventional synthetic DMARDs such as methotrexate and hydroxychloroquine or sulfasalazine are acceptable provided all drugs comprising the combination meet stability requirements. Dose adjustments for management of toxicity of the above medications are allowed and should be documented, along with documentation of the AE which led to the change in the medication.

Risks associated with conventional synthetic DMARDs are identified in the labeling supplied with these drugs and should be reviewed with the subject.

Note: Temporary, perioperative changes in background RA therapy are allowed at the discretion of the Co-PI Rheumatologist and the Co-PI Surgeon to reduce the risk of potential bleeding, infection, or delayed wound healing related to the implant procedure. Such changes are considered standard of care.

All changes in background therapy shall be noted on the Concomitant Medication Log.

14.3 Allowed Medications

The following medications are allowed during study participation:

- Glucocorticoids at the equivalent of ≤ 10 mg prednisone daily may be continued at a dose documented to have been stable within 14 days prior to informed consent and until Week 12.
- NSAIDs: over the counter may be continued and those by prescription listed below at the approved dose for RA documented to have been stable within 14 days prior to informed consent and until Week 12:
  - Celecoxib (Celebrex)
  - Diclofenac (Voltaren, Cataflam)
  - Diflunisal (Dolobid)
  - Etodolac (Lodine)
  - Flurbiprofen (Ansaid)
  - Ibuprofen (Motrin)
  - Indomethacin (Indocin)
  - Ketoprofen (Orudis, Oruvail)
  - Ketorolac (Toradol)
  - Meloxicam (Mobic)
  - Nabumetone (Relafen)
  - Naproxen (Anaprox, Naprelan, Naprosyn)
  - Piroxicam (Feldene)
- Mild oral opiates (i.e., acetaminophen-codeine [Tylenol 1, 2, 3], tramadol [Ultram], pentazocine [Talwin], hydrocodone [Vicodin, Lortab]) taken as needed to treat pain. Must not be taken 24 hours prior to RA disease activity assessments.

Note: Mild oral opiates taken on a regular basis to treat pain may be continued at a dose documented to have been stable within 14 days prior to informed consent.

Initiating or changing any of the above listed glucocorticoids, NSAIDs or oral opiates after study entry and until completion of Week 12 assessments is not allowed. Any change must be noted on the Concomitant Medication Log.

Temporary, perioperative changes to any of the above listed medication is allowed at the discretion of the Co-PI Surgeon to reduce the risk of potential bleeding, infection, delayed wound healing, or post-operative pain related to the implant procedure. Such changes are considered standard of care and shall be noted on the Concomitant Medication Log.

14.4 Prohibited Medications and Interventions

The following medication and interventions are prohibited:

- Steroid pulse therapy through completion of Week 12 assessments
- Biologic or targeted synthetic DMARDs through completion of Week 12 assessments
- Intra-articular corticosteroid injection through completion of Week 12 assessments
- Ionic or nonionic linear chelated gadolinium-based contrast agents for MRI studies such as gadodiamide, gadoversematide, gadofosvest trisodium, gadoxetate disodium, gadopentate dimeglumine, and gadobenate dimeglumine

The following interventions are prohibited for subjects with an implanted MicroRegulator:

- External electrical stimulation devices (e.g., TENS units) on the neck
- Electrically active implantable medical devices (e.g., cardiac pacemakers, automatic implantable cardioverter-defibrillators)
- Extra-corporeal shock wave lithotripsy in the cervical spine region
- Short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy. Diagnostic ultrasound is not included in this contraindication
- Electrosurgery (electrocautery or radio frequency ablation devices) in the cervical spine region
- Monopolar electrocautery
- Any investigational therapy
- Therapeutic radiation

In the event a subject requires any of the above interventions, MicroRegulator must be suspended (see Section **11.8**), decommissioned (see Section **11.9**) or explanted (see Section **11.10**), as applicable. In the event therapy is suspended or decommissioned, subject should continue to follow the regular visit schedule and adhere to all study procedures and will be followed for safety.

14.5 Rescue Treatment

Additional treatment for RA is only allowed after completion of Week 12 assessments in the event the subject experiences worsening of RA symptoms or if the subject does not experience adequate clinical improvement. If additional RA treatment must be provided prior to Week 12, this is considered rescue treatment and will be reported as a protocol deviation. Not allowing additional treatment until after Week 12 is consistent with contemporaneous drug studies and "FDA's Draft Guidance for Industry Rheumatoid Arthritis: Developing Drug Products for Treatment (Draft Guidance May 2013)" because it ensures sufficient time for evaluation of clinical response to investigational treatment.

After completion of Week 12 assessments, additional treatment for RA may be provided at any time. The decision about the need, type and timing of treatment is left to the discretion of the Co-PI Rheumatologist and the subject. The Co-PI Rheumatologist will take into consideration in their

decision the available results from RA disease activity assessments, subject's medical history and information in the labeling of the treatment being considered.

IMPORTANT: The Co-PI Rheumatologist shall discuss with the subject risks associated with the treatment chosen, **particularly any black box warnings included in the label for the prescribed treatment in the context of each subject's medical history and comorbidities**. If there are additional monitoring or testing required to help mitigate such risks, this shall also be discussed with the subject. The Co-PI Rheumatologist shall refer to the Medication Guide Database for current safety information related to the treatment chosen (https://www.fda.gov/drugs/drug-safety-and-availability/medication-guides). This information shall be reviewed with the subject and the subject shall be informed that the guide will be provided to them at the pharmacy when the drug is dispensed.

Note: On September 1, 2021, FDA issued a drug safety communication specific to JAK inhibitors. It is important that the Co-PI Rheumatologist is aware of this information if considering a JAKi for the subject's treatment. This information is provided in ***Appendix B*** *and can also be located at the following website:*

https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death

This information shall be provided to the subject if a JAKi is chosen as treatment.

Both the Co-PI Rheumatologist and subject will remain blinded to original treatment assignment when making this treatment decision. Blinding is maintained until the dataset for primary analysis is locked, and the study data are unblinded.

Additional treatments considered as rescue are RA disease modifying drugs that may include, but are not limited to:

- Addition of a biologic or targeted synthetic DMARD
- Dose increase of the ongoing conventional synthetic DMARD background therapy or addition of another conventional synthetic DMARD
- Addition or dose increase of a corticosteroid (equivalent to an average daily use $>$ 10 mg prednisone/day between study visits);
- A corticosteroid injection within 30 days of a study visit.

The need, timing, type and reason for rescue treatment are recorded on the follow-up visit and Concomitant Medication CRFs and entered into the EDC.

Subjects initiating rescue treatment prior to Week 12 will be imputed as non-responders in the analysis of primary and key secondary efficacy endpoints. The initiation of these treatments with study treatment during open-label follow-up is considered "augmented therapy" since it is allowed at the discretion of the Co-PI Rheumatologist and the subject after Week 12. Subjects

treated with augmented therapy will be evaluated as a subgroup for the purpose of exploratory efficacy analysis (see Section **17.7**).

Subjects that are rescued or receiving augmented therapy will continue to receive their assigned study treatment unless suspension of stimulation is judged necessary by the Co-PI Rheumatologist and the subject (see Section **11.8**).

Subjects that receive rescue treatment or augmented therapy are expected to continue adhering to the study follow-up visit schedule, complete the study procedures, and to be monitored for safety.

15 ASSESSMENT OF SAFETY

15.1 Specifications of Safety Parameters

Adverse events (AEs) for each subject from the time the subject gives written informed consent through Week 264 (end of study) will be recorded in the EDC system and monitored. Each AE will be evaluated by clinical investigators in terms of seriousness, severity (i.e., mild, moderate, severe) and strength of relationship (i.e., not related, unlikely related, probably related, definitely related, indeterminate) to the implant device, implant procedure, explant procedure, Energizer and stimulation therapy. Each AE will be reviewed by sponsor in accordance with sponsor's SOP. The study sponsor is responsible for ensuring that all AEs are appropriately recorded, adjudicated and, when applicable, reported to the government(s), ethics committee(s) and other study centers per applicable regulations. The sponsor will also appoint an independent Data Monitoring Committee (DMC) for ongoing monitoring of subject safety (see Section **18.2.5**). Subjects with RA experience a persisting set of symptoms associated with the disease and may continue to present with a wide range of symptoms during the recovery process after the implant procedure. Subjects healing appropriately may suffer from acute infections and/or inflammatory exacerbations unrelated to the procedure due to the natural course of their RA. Therefore, clinical investigators will evaluate the occurrence of AEs, excluding usual post-operative recovery signs and symptoms experienced by study subjects, unless corroborated by objective findings and/or requiring specific medical or therapeutic interventions (e.g., antibiotics).

15.2 Classification of AEs

15.2.1 AE severity

All AEs will be reported from the time of consent through study exit. All AEs will be categorized in terms of their severity as:

- *Mild.* Event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities
- *Moderate.* Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment

- *Severe.* Event results in significant symptoms that prevents normal daily activities; may require hospitalization or invasive intervention

15.2.2 AE causality

The relationship of all AEs to the implant procedure, explant procedure, implant device, Energizer and stimulation will be evaluated by Co-PIs and categorized as:

- *Definitely related*. There is a clear temporal association, and no other possible cause.
- *Probably related*. There is a clear temporal association, and a potential alternative etiology is not apparent.
- *Unlikely related*. The AE does not follow a reasonable temporal association; or causal relationship with the device or procedure involved in the research is unlikely but cannot be completely ruled out.
- *Not related*. The AE is completely independent of the study investigational device, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the investigator.
- *Indeterminate*. Information gathered about the AE is not sufficient to arrive at a definite conclusion about causal relationship.

Any AE that is determined to be definitely related or probably related to the study investigational device or procedure will be categorized as device related. Once the study dataset is locked for primary analysis and the study is unblinded, if a subject was assigned to the control group but has an AE reported as related to stimulation, the AE relationship will be updated to "not related."

15.2.3 AE expectedness

It is sponsor's responsibility to evaluate expectedness of each device-related AE in accordance with sponsor's standard operating procedure (SOP). Expectedness is categorized as either:

- *Expected*. AE is consistent with the risk information described in the ICF, IFU and clinical investigational protocol (see Section **16**); or
- *Unanticipated or unexpected*. AE is considered UADE or USADE if it is not consistent with the risk information described in the ICF, IFU and clinical investigational protocol (see Section **16**).

15.3 AE Adjudication

AEs are reviewed by the sponsor on a regular, ongoing basis. Each AE will be reviewed by sponsor in accordance with the sponsor's SOP. The study sponsor is responsible for ensuring that all AEs are appropriately recorded, adjudicated and, when applicable, reported to government(s),

ethics committee(s) and other study sites, per applicable regulations. The following is reviewed for each AE:

- Need for clarification or additional information from the site
- Appropriateness of classifications for severity, causality and expectedness
- If the adverse event is unanticipated, determination as to whether it poses unreasonable risk of harm to study subjects if it were to reoccur; and
- Requirements for reporting to the FDA and site IRB based on the nature of the event.

Outputs of reviews are filed by sponsor, and action items are tracked to resolution.

If the investigator and sponsor do not agree on the seriousness or causality of an event, the event will be reviewed by an independent adjudicator, who is a qualified medical expert. The adjudicator is blinded to treatment assignment and will have access to the following:

- AE information reported in the EDC system
- A list of potential risks associated with the implant device, implant procedure, explant procedure and stimulation therapy
- Information provided by investigators, including clinical notes, laboratory results, concomitant medications, and medical/surgical history; and
- Clinical outcome measures reported in the EDC system.

The independent adjudicator may request further information if this is required to complete AE review. The adjudicator will confirm their determination of seriousness and causality of the event. The adjudicator's decision is considered as final and is recorded in the EDC system and used in all analyses.

In accordance with the DMC Charter, all AEs are reviewed by the DMC on an ongoing, regular basis, with *ad-hoc* reviews occurring within 5 working days of sponsor notification of any subject death or SAE related to the implant procedure, explant procedure, implant device, or stimulation. The DMC review meetings and recommendations will be documented in meeting minutes and filed in accordance with the DMC Charter.

15.4 Guidelines for Reporting of AEs

All AEs, regardless of seriousness or relationship to the investigational device, will be recorded in the EDC system and will include event description, date of onset, investigator's assessment of severity, relationship to investigational device, and date of resolution/stabilization of the event. All AEs will be followed through end of the study or through study exit of individual subject.

Any pre-existing medical condition that is present at the time of Screening will not be reported as an AE, unless there is a worsening of that condition. The occurrence of diagnostic or elective

surgical procedures for a pre-existing condition will not be recorded as an AE, unless the condition becomes more severe or results in an AE.

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The investigator should specify the date of onset, severity, action taken with respect to the investigational device, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the investigational device.

The investigator should take appropriate measures to follow all AEs until resolution or until progression has been stabilized, or until study exit, to ensure the safety of the subjects. If the AE continues beyond the last planned visit per protocol and/or the subject withdraws from the study, clinical investigators should follow the subjects according to standard of care.

All AEs must be reported to sponsor based on the following timeline:

Type of AE	Reporting Schedule to Sponsor
Subject death	Within 24 hours from becoming aware followed by a written report within 2 working days
SAE (SAE/SADE/UADE/USADE)	Within 24 hours from becoming aware followed by a written report within 4 working days
Device-related AE	Within 24-48 hours from becoming aware

The investigator will report the above to the reviewing IRB per the IRB's guidelines. The study sponsor is responsible for reporting safety events to the FDA as required per 21 CFR 812 and to IRB per the IRB's guidelines.

All SAEs (SAE/SADE/UADE/USADE) will be followed until satisfactory resolution, until the investigator deems the event to be chronic, or until the subject exits the study. Other supporting documentation of the event may be requested by the sponsor and should be provided as soon as possible.

16 RISK/BENEFIT ASSESSMENT

16.1 Assessment of Risks for the Proposed Investigation

VNS therapy for the treatment of RA has risks associated with the surgical procedure required to implant the stimulation device and with the electrical stimulation itself. The risks are discussed in detail later in this section. These risks have been evaluated in animal studies, in the proof-of-concept study in RA subjects implanted with the Cyberonics VNS Therapy System (SPM-005), and in the pilot study of the SetPoint System (SPM-008) (see Section **7.3**). The risks are potentially severe, and the likelihood of AEs related to the device is only partially understood. Risk mitigation procedures include careful selection of eligible subjects, the use of specialized, highly experienced investigators, including neurosurgeons with previous surgical experience

using approved VNS devices and rheumatologists with extensive clinical trial experience. A formal training program will be required for all surgeons who participate in this study to ensure adequate experience. Device programmers will undergo formal training as well.

The assessment of risk is informed by long-term follow-up studies of patients who have had FDA approved VNS devices implanted for treatment of drug refractory epilepsy or treatment resistant depression. These studies reveal complication rates of < 5%. Complications include post-operative infections, device failure due to lead fracture, hoarseness, dysphasia, dysphonia, and vocal cord paralysis. In rare instances, the device had to be removed (Aalbers 2015). VNS devices were approved for use 20 years ago, and more than 100,000 VNS devices have been implanted in more than 80,000 patients (Revesz 2016). As such, there is an extensive safety record for VNS devices in non-immunosuppressed patients with seizure disorders or depression.

It is possible that the likelihood of infection for an implanted VNS device will be higher in an RA patient population given the disease causes inflammation and that immunosuppressive drugs are routinely prescribed, such as methotrexate, steroids and TNF inhibitors.

16.2 Potential Risks with VNS Therapy

Due to the novel application of the VNS therapy using the SetPoint System, risks are based on the FDA-approved VNS devices implanted for treatment of drug refractory epilepsy or treatment resistant depression. The most common side effects reported by patients implanted with a commercially available VNS device are:

- Transient coughing during VNS stimulation
- Neck pain
- Hoarseness or other voice disturbances (dysphonia) during VNS stimulation
- Shortness of breath (dyspnea)
- Throat pain, a burning sensation, or inflammation of the back of the throat (pharyngitis)
- Swallowing difficulties (dysphagia). Swallowing difficulties could lead to aspiration
- Tingling, prickling or numbness near the implant site (paresthesia)
- Nausea and indigestion

In those patients, these symptoms generally occurred only during the time the device was delivering electrical stimulation. Flu-like symptoms and dizziness were also reported (Kahlow and Olivecrona 2013). Other uncommon side effects reported include:

- Scarring or infections of the tissues around where the device is implanted.
- Worsening of certain lung and breathing diseases such as asthma, and chronic obstructive pulmonary disease in patients who already had these diseases before the device was implanted

- Movement of the device from where it was placed by the surgeon and damage to the vagus nerve, other nerves, blood vessels, or other structures of the body
- The device, or any of its parts, breaking and not delivering stimulation correctly
- Worsening or new onset of sleep apnea
- Prolonged hoarseness due to damage by the device to the nerve fibers supplying the muscles of the throat
- Slowing or other alterations of the heart rate
- Headaches
- Flushing
- Vomiting
- Gagging
- Eructation
- Constipation
- Syncope
- Weight change (loss or gain)

In the long-term extension of the SetPoint System pilot study (SPM-011), 1 subject experienced severe neutropenia. Although the event was classified as being related to the subject's RA, the presentation and resolution coincided with changes in the subject's stimulation regime. Because of this, investigational VNS could not be completely ruled out as a potential cause.

16.3 Potential Risks with Surgical Implantation

Surgical placement of the implant device can cause damage to the vagus nerve. While the damage typically heals with time, in rare cases it can be permanent. The most significant symptoms from damage to the vagus nerve are hoarseness or other voice changes, breathing or swallowing changes. Swallowing difficulties could lead to aspiration. These risks could occur because nerves that control some throat muscles and the vocal cords come from the vagus nerve.

In rare cases, during the surgery for device placement, other muscles, nerves, blood vessels or tissues in the area can be damaged. Damage to sympathetic innervation to the orbit can result in Horner's Syndrome which includes symptoms of ptosis, meiosis, and anhidrosis. Damage to the vocal cord can result in vocal cord paralysis. Symptoms of vocal cord paralysis include voice changes and difficult breathing, which generally resolve with surgical intervention and voice therapy.

Other risks associated with surgical implantation of MicroRegulator include:

- Complications related to general anesthesia with endotracheal intubation;

- Postoperative pain, redness, itching, swelling or seroma at the implant site;
- Eructation, constipation, vomiting or gagging
- Excessive bleeding due to unanticipated vessel injury; and
- Scarring or infection of the tissues around where the device is placed. Infections usually treated with antibiotics, in rare cases requiring explantation.

The risks associated with the explant procedure in the event the device requires removal needs to be factored into the overall risk assessment when evaluating participation in the clinical study. The safety and impact on vagus nerve function post-device explant is unknown. Preclinical studies in canines show no evidence of implantation site and device fibrosis and vagus nerve viability appears unaffected as assessed by morphologic and histopathologic examination including stains for myelin integrity.

16.4 Potential Risk Due to Concomitant Use of csDMARDs and/or Additional RA Treatment

Risks associated with conventional synthetic DMARDs identified in Section **14.2** and/or additional RA treatment are identified in the labeling supplied with these drugs. It is unknown if these risks are increased by concomitant use with VNS therapy.

IMPORTANT: The Co-PI Rheumatologist shall discuss with the subject risks associated with the treatment chosen, **particularly any black box warnings included in the label for the prescribed treatment in the context of each subject's medical history and comorbidities**. If there are additional monitoring or testing required to help mitigate such risks, this shall also be discussed with the subject.

16.5 Potential Risk Due to Contrast Enhanced MRI

The implanted MicroRegulator may exhibit force, torque, heating and vibration effects due to the static magnetic field, gradient magnetic and radio frequency fields in an MRI environment, which may be perceived as a slight tugging, vibration or heating sensation at the implant location while in or near an MRI scanner.

There is a risk of nephrogenic systemic fibrosis from exposure to gadolinium-based contrast agents used for enhanced MRI imaging of the hand, which is performed as part of the study assessments. Nephrogenic systemic fibrosis is a syndrome that occurs in patients with renal failure due to the decreased excretion of gadolinium ions and deposition of a gadolinium-phosphate precipitate in organs, causing fibrosis (Olchowy 2017). The exclusion of subjects from the study having decreased eGFR is therefore mandated. Additionally, the deposition of gadolinium-based contrast agents (GBCA) in the brain has been observed even in patients with normal renal function, though the clinical significance is unknown (Murata 2016, Olchowy 2017). In several retrospective studies, those patients that had been exposed to linear open-chain chelated GBCAs had increases in MRI evidence of brain deposition of gadolinium, whereas those that had

been exposed to macrocyclic chelated GBCAs did not (Cao 2016, Kanda 2015, Radbruch 2015). Because of this, the subjects will not be allowed to receive linear open chain chelated GBCAs, and they must instead receive a macrocyclic chelated GBCA (see Section **14.4**).

16.6 Risk Analysis of the SetPoint System

For this pivotal study, a cross-functional team at SetPoint Medical performed a systematic risk analysis in accordance with BS EN ISO 14971:2012 to identify foreseeable sequences of events that could lead to hazardous situations when using the SetPoint System. These situations were then correlated to potential harms. Additional reasonably foreseeable harms beyond those identified above include:

- Electrocution caused by malfunction or misuse of Energizer or Wireless Charger;
- Critical tissue damage caused by a malfunction of Energizer that results in unsafe radio frequency exposure or a burn;
- Critical tissue damage caused by a malfunction of Energizer that results in delivery of unsafe stimulation levels;
- Critical tissue damage caused by damage to the implant;
- Asphyxiation caused by misuse of Energizer;
- Stroke caused by the implant migrating and obstructing a blood vessel;
- Death due to radio frequency emissions interference between the SetPoint system and some other life-sustaining equipment; and
- Catastrophic failure of the battery causing harm or severe injury, including death.

16.7 Benefit Assessment of the Proposed Investigation

RA patients who have had inadequate responses or who are intolerant to biologic or targeted synthetic agents are the target study population for this pivotal study. These patients can be rotated on to other drugs with different mechanisms of action which may be effective in reducing disease activity, based on RCTs in patients who have failed at least 1 biologic or targeted synthetic DMARD. However, subjects who are prone to adverse side effects, such as infections, may not be able to tolerate other drugs with different mechanisms of action because they all impair host response to infection. For such subjects, VNS may be an appropriate and effective therapeutic choice.

Initial data from the SPM-008 pilot study demonstrated clinically relevant reductions in RA disease activity in highly drug refractory patients when the investigational VNS device was activated. Reduction in clinical disease activity was documented in subjects who received active stimulation (**Figure 14**). Of note, 5 out of 10 subjects in the actively stimulated groups exceeded MCID in DAS28-CRP at 12 weeks and achieved EULAR good or moderate responses. Two subjects achieved DAS28 remission. Both had been diagnosed with RA 49 and 13 years prior to

enrollment and had incomplete responses to prior treatment with 4 different biologic or targeted synthetic DMARDs.

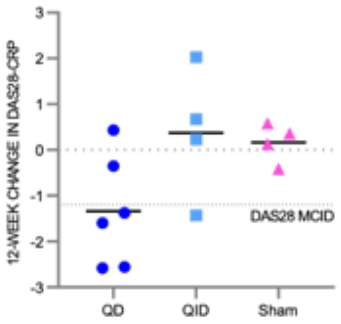
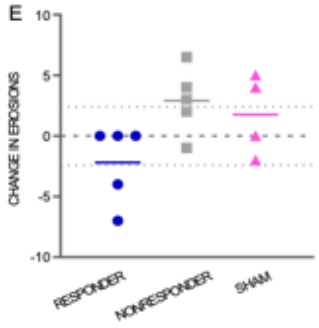


Figure 14: SPM-008 Individual DAS28-CRP Score Change from Baseline to Week 12

An improvement in the RAMRIS bone erosion scores correlated with a clinically meaningful response in DAS28-CRP (**Figure 15**), which is a particularly encouraging preliminary finding in this highly drug-refractory population.



Dotted line at -1.2 represents the MCID of DAS28-CRP change

Figure 15: SPM-008 Change in RAMRIS Bone Erosion Score by DAS28-CRP Response

In addition, reduction in levels of proinflammatory cytokines and improvements in RA disease activity scores observed in the pilot study after 12 weeks of therapy, were similar with improvements observed in the European proof-of-concept study (SPM-005/006).

Complete results from the initial study were filed in a final study report with FDA in April 2019 (G170231/R002).

16.8 Consideration of Patient Preference

Given the limited therapeutic treatment options for patients who failed or are intolerant to biologic DMARDs, patients are expected to have a high-risk tolerance for considering new therapeutic modalities like VNS. There are currently multiple biologic DMARDs which target TNF, IL-6, CTLA-4 cell signaling, IL-1, Janus Kinase and B-cell depletion. Patients who failed or are

intolerant to biologic DMARDs might choose to continue therapy with approved drugs with alternative molecular targets. All of these targeted agents carry a 1.5-2-fold higher risk of infection and require repetitive parenteral administration (infusion or SC injections), except JAKi that are taken orally (Listing 2013). These alternative drugs are expensive, and patient drug adherence is an issue given the parenteral route of administration for most of the therapeutic options.

Other alternatives for therapy include oral glucocorticoids, which can increase the risk of infection and have a negative effect on bone and cartilage. Patients might prefer to volunteer to participate in RCTs of experimental agents to treat RA but must accept the fact that they could be randomized to the placebo arm during the conduct of the trial. Many drug refractory RA patients who do want to participate in clinical trials are excluded from participation because their acute phase ESR or CRP is below the minimum threshold for entry despite the presence of multiple swollen and tender joints on physical exam. These excluded patients might want to pursue alternative approaches to therapy with a VNS device.

In addition, patients with RA are at increased risk for malignancies, including lymphoma, compared to the general population (Wilton and Matteson 2017). Factors associated with this increased risk of cancer include use of immunosuppressive drugs used to treat RA. Patients with the highest levels of disease activity appear to be at greatest risk for malignancy. Therefore, RA patients with poorly controlled disease need to decide what, if any, therapeutic option they want to choose given the association of disease activity with an increased risk of cancer.

16.9 Assessment of Uncertainty

There is uncertainty with respect to the relative safety of the SetPoint System versus alternative approved therapies, as well as its anticipated degree of efficacy. While the preclinical and limited clinical data are encouraging, there is a clear need to study and document clinically meaningful responses in a controlled trial with longer term follow-up.

17 STATISTICAL CONSIDERATIONS

Two detailed Statistical Analysis Plans (SAP) will be prepared for the primary analysis through Week 12 and the open-label, long-term follow-up prior to a formal interim analysis at the end of Stage 1. Following is a description of the study sampling plan and a summary of the intended analyses.

17.1 Randomization

After completing Day 0 assessments, all enrolled subjects will be assigned in a 1:1 ratio to either the treatment or the control group. The randomization will be stratified to help ensure balanced distribution between treatment groups of subjects with: inadequate response or loss of response to JAKi; inadequate response or loss of response to ≥4 biological DMARDs (bDMARDs) with ≥ 2 mechanisms of action; and those with < 4 TCJ28 or < 4 SJC28 at Day 0. The randomization scheme will be generated by the study biostatisticians and implemented centrally through an IRT.

17.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the difference between treatment and control groups in the proportion of subjects achieving the ACR20 response at Week 12 from baseline on the day of informed consent. The primary efficacy analysis will be performed on the ITT population (see Section **17.8**) using pooled data from Stage 1 and 2.

The hypothesis of interest is:

H_0: $p_t - p_c = 0$

H_1: $p_t - p_c > 0$

where p_t is the response rate in the treatment group and p_c is the response rate in the control group. The study will test the null hypothesis (H_0) that there is no difference between the treatment and control groups in the proportion of subjects 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 will be considered successful if there is a statistically significant improvement in the proportion of subjects with ACR20 response in favor of the SetPoint System.

The sample size is calculated based on an estimated 60% response rate in the treatment group and 30% response rate in the control group. A sample size of 250 subjects, 125 in each group, offers 96% power to detect a difference of 30% at the one-sided alpha of 0.025. If the true response rates are 50% in the treatment and 30% in the control group, the sample size of 250 subjects has 77% power to detect a difference of 20% at the one-sided alpha of 0.025. Additional power calculations for 250 subjects using estimated response rates of 20 to 40% in control and 35-70% in treatment are provided in **Table 4**. Table 4 also shows power if enrollment ends at 240 subjects. The decrease in power is <1% for all scenarios and most often <0.5%.

Table 4: Power Calculations for ACR Response Based on Pooled Data from Stage 1 and 2

Control (%)	Treatment (%)	Difference (%)	Power N = 250	Power N=240
20	50	30	0.967	0.966
20	45	25	0.917	0.916
20	40	20	0.812	0.807
20	35	15	0.609	0.601
30	60	30	0.959	0.959
30	55	25	0.900	0.898
30	50	20	0.773	0.770
30	45	15	0.555	0.549
40	70	30	0.959	0.958
40	65	25	0.897	0.893
40	60	20	0.762	0.750

Power based upon 1,000,000 simulations per scenario.

17.3 Interim Analysis

One formal interim analysis is planned at the end of Stage 1 when the approximately 60 randomized subjects enrolled in Stage 1 have reached their Week 12 endpoints. The interim analysis will be performed on the Stage 1 ITT population. The purpose of this interim analysis is to check for safety risks and a lack of efficacy prior to enrolling subjects in Stage 2. No early success stopping may possibly occur. Therefore, there is no alpha-spending as there is no possibility for early claim. As these data contribute to the overall device experience for the safety review, and no early success stopping is permissible, no Type I error inflation occurs with such interims.

The DMC and FDA will review the 12-week unblinded data from Stage 1, including demographics, efficacy, safety, enrollment rates, and device implantation rates, and determine whether the following stopping rule is met:

- The difference between treatment and control in the proportion of subjects achieving the ACR20 response at Week 12 from baseline on the day of informed consent is less than 10%.

This stopping rule in 60 subjects balances the need to stop a trial with a projected low probability of success with a need to avoid prematurely stopping a potentially successful trial after Stage 1, given the decision is based on a dichotomous endpoint in a relatively small number of subjects.

For illustrative purposes, **Table 5** provides stopping probabilities for 60 subjects and their effect on power in 250 subjects, using an estimated ACR20 response rate of 30% in the control group and a range of 35-60% in the treatment group. The proposed stopping rule has a 50% probability of stopping a study having < 30% power to meet the primary efficacy objective in 250 subjects. Type 1 error is maintained at 2.5% even without the futility stop. The last column in the table

shows power if enrollment ends at 240 subjects. Again, the power decreases by < 1% in all scenarios.

Table 5: True Probability of Stopping after Stage 1 and Power of Study Success Based on Pooled Data

Control (%)	Treatment (%)	Probability of Stopping N = 60 (Stage 1)	Power N = 250 (Stage 1 + 2)	Power N = 240 (Stage 1 + 2)
30	60	0.040	0.959	0.959
30	55	0.089	0.900	0.898
30	50	0.173	0.773	0.770
30	45	0.293	0.555	0.549
30	40	0.444	0.291	0.282
30	35	0.608	0.096	0.093

Operating characteristics calculated by simulating 1,000,000 trials per scenario using chi-square test.

Conversely, with this stopping rule, there is 17% probability of stopping a study having 77% power to detect a 20% difference, highlighting the need for a balanced approach on stopping rules based on a dichotomous endpoint with just 60 subjects.

Based on their review, the DMC will convey their decision to terminate the study if the stopping rule is triggered or continue to Stage 2 as planned to the Chief Executive Officer (CEO) of SetPoint Medical or a designee. In the event the stopping rule is triggered, the CEO or designee will notify the FDA about the DMC's decision and the study will be terminated. The study will be unblinded, and all Stage 1 data analyzed. The sponsor will submit to the FDA a report with the DMC's decision together with the datasets, programs and program outputs as well as any proposals for further clinical research. If the stopping rule is not triggered, the sponsor will initiate an IDE Supplement to the FDA to request initiation of Stage 2 enrollment, and providing the name and contact information of the independent statistician from whom the FDA will request the Interim Report containing unblinded data. The unblinded data will be provided directly to the FDA upon request, maintaining blinding of the sponsor. The study will advance to Stage 2 only after receiving approval from the FDA.

The DMC will continuously monitor subject safety throughout Stages 1 and 2 and can stop the study anytime if serious safety concerns arise, as detailed in the DMC Charter.

17.4 Analysis of Key Secondary Endpoints

To support potential device labeling claims, a subset of secondary endpoints will be identified and analyzed using appropriate methods for controlling for family-wise type-1 error rate (FWER). This will be detailed in the SAP that will be submitted to the agency prior to the formal interim analysis.

17.5 Analysis of Exploratory Endpoints

To gather additional efficacy data and long-term safety.

17.6 Analysis of Safety Measures

The incidence of AEs and SAEs from informed consent to Week 264 will be tabulated. Each AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and presented based on the system organ class and preferred term.

17.7 Handling of Rescue Treatment

Subjects that initiate a rescue treatment prior to Week 12 (see Section **14.5**) will be imputed as non-responders in the analysis of primary and key secondary efficacy endpoints (e.g., no ACR20 response, no DAS28-CRP good/moderate EULAR response, no DAS28-CRP response, and no HAQ-DI response). Additional, exploratory, subgroup analysis will be presented for subjects combining additional RA treatment with VNS during open-label follow-up (i.e., augmented therapy).

17.8 Analysis Populations

The interim and primary efficacy analyses at Week 12 will be conducted on the intent-to-treat (ITT) population. Exploratory analyses will be performed on the ITT and per-treatment-evaluable (PTE) populations through Week 12 and on the open-label and cross-over PTE populations during the open-label, long-term follow-up. The safety will be evaluated on the safety population. All analysis populations are defined below:

- *ITT population*. All enrolled and randomized subjects in Stage 1 and 2.
- *PTE population*. Subjects from ITT population who received the assigned treatment through Week 12, have no major procedural protocol deviations (see Section **18.2.2**), and for whom follow-up data through Week 12 are available.
- *Treatment to Open Label (TOL) population*. Treatment subjects 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.
- *Control to Open Label (COL) population.* Control subjects from ITT population who received non-active (sham) stimulation through Week 12, 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.
- *Safety population.* All enrolled subjects.

18 STUDY MANAGEMENT

18.1 Ethical Considerations

The rights, safety and well-being of subjects shall be protected in accordance with the ethical principles based in the Declaration of Helsinki and consistent with ISO14155, 21 CFR Parts 11, 50, 54, 56, and 812 Good Clinical Practice, all IRB requirements and all applicable local laws and requirements. All parties are responsible for ethical conduct of the study in accordance with their respective roles in the investigation. The sponsor and the investigators shall avoid improper influence or inducement of the study subject, monitor, the clinical investigator(s) or other parties participating in or contributing to the clinical investigation.

18.2 Sponsor Responsibilities

SetPoint Medical, as the study sponsor, has the overall responsibility for the conduct of the study and will ensure that the study is conducted under the guidance of ICH Good Clinical Practice (E6), Clinical investigation of medical devices for human subjects – Good clinical practice (BS EN ISO 14155) and other applicable local and federal (e.g., 21 CFR Parts 11, 50, 54, 56, and 812) regulations, including the archiving of essential documents. A list of the names, locations, and chairpersons of all IRBs (including actions taken by each IRB on the protocol) that have been or will be asked to review the protocol will be kept on file. Qualified personnel who participate in the conduct of this clinical trial will be qualified by education and/or experience and trained to perform their tasks. The sponsor will maintain a list of names and addresses of all investigational sites at which the investigation will be conducted and central labs providing study-related services under a separate cover. The study will not use, in any capacity, the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this clinical study.

18.2.1 Training

Sponsor personnel or designee will provide all clinical investigators with training on use of the SetPoint System prior to their participation in the clinical study.

The study staff involved will undergo site initiation and training related to their delegated responsibilities, which will include:

- Clinical investigational protocol SPM-020
- SetPoint System
- Concomitant medication
- Central laboratory procedures
- Safety and AE reporting
- Device deficiency reporting

- Compliance reporting
- Investigator responsibilities (GCP)
- Device accountability
- Authorization process
- EDC and IRT systems
- Study binders
- Monitoring

New members of the investigation site team may be added from time to time at new or existing sites. New personnel should only start their assignment after receiving adequate training in the clinical investigation requirements and this training shall be documented. The names, initials, signatures, functions, and designated authorizations of new site personnel shall be documented.

18.2.2 Protocol deviation

All efforts should be made to avoid any protocol deviation. Any deviation from the requirements outlined in this protocol will be considered a protocol deviation. Protocol deviations will be categorized as major procedural if a study subject:

- Undergoes any study-related procedure before signing an IRB-approved informed consent form, or
- Receives study treatment not consistent with the treatment assignment, or
- Is no longer eligible but received study treatment.

A protocol deviation that may affect the scientific soundness of the protocol or the rights, safety, or welfare of the patients should be reported to the sponsor and the IRB as required. Other deviations are those that occur in direct association with a specific study patient. These include, but are not limited to, deviations from the informed consent process, inclusion/exclusion criteria, protocol-specified procedures and assessments, and investigational device handling and usage. All protocol deviations and their reasons will be reported promptly to the study sponsor and documented in the study database.

The following information shall be provided promptly to the sponsor and as per IRB guidelines: requests for deviations, and reports of deviations, if the deviation affects subject's rights, safety and well-being, or the scientific integrity of the clinical investigation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the IRB. Such deviations shall be documented and reported to the sponsor and the IRB as required. Unavoidable protocol modifications may be required due to COVID-19 illness and/or COVID-19 control measures (see Section **19**). Efforts will be made to minimize impacts of protocol deviations on study integrity.

18.2.3 Device deficiency

Any device deficiency related to the identity, quality, durability, reliability, safety or performance of an investigational medical device, including device malfunctions, use errors, and inadequate labelling shall be documented throughout the clinical investigation, investigated by the study sponsor, and reported to appropriate regulatory bodies and IRB as applicable. Also, all device deficiencies that do not lead to an AE but could have led to a medical condition if either suitable action had not been taken, intervention had not been made, or circumstances had been less fortunate shall be reported.

18.2.4 Data monitoring

Study site monitoring will be performed by trained and qualified CRAs from the study sponsor and contract CRAs who will be trained and qualified by sponsor. Study sites will be visited regularly to ensure that the study is conducted in compliance with 21 CFR Parts 11, 50, 54, 56, 812, ISO 14155, the study protocol and other applicable regulations. Study monitors will also ensure that the data reported in the EDC system is consistent with the information found in the subject's medical records and source documents (source data verification). Monitoring will include assessment of the site's overall progress, including, but not limited to, the site's ability to keep accurate records and to report study related data, including AEs, to the study sponsor in a timely fashion. A detailed monitoring plan will be developed and maintained by the sponsor.

18.2.5 Data Monitoring Committee

The sponsor will appoint an independent DMC to ensure compliance and proper clinical study monitoring. The DMC will be responsible for safeguarding the interests of study subject, assessing the safety and efficacy of the interventions during the trial, and for ongoing monitoring of the overall conduct of the study. During Stage 1 enrollment, the DMC will meet after enrollment of 15, 30, 45, and 60 subjects. During Stage 2 enrollment, the DMC will meet once every 3 months. Following completion of Stage 2 enrollment, the DMC will meet once every 6 months.

The DMC will provide recommendations about stopping or continuing the study based on their ongoing review of cumulative safety and efficacy data and at the end of Stage 1 based on a formal interim analysis of the Week 12 safety and efficacy data (see Section **17.3**).

Early termination considerations will generally apply only to emerging safety issues of major concern, or problems with trial conduct that suggest the trial could not be completed successfully with a reliable conclusion in a feasible time frame. To contribute to enhancing the integrity of the trial, the DMC may also formulate recommendations relating to improving adherence to protocol-specified regimens and retention of participants, and the procedure for data management and quality control. The responsibilities of the DMC are further detailed in the DMC Charter.

18.2.6 Data management responsibilities

Data management will be performed by the study sponsor.

EDC System

A validated and 21 CFR Part 11 compliant EDC system will be used as the study database. The system will undergo validation to confirm study-specific configuration and user acceptance testing (UAT) prior to release. The validation, testing and release documentation will be maintained on file by the study sponsor. Data entry will be performed by site personnel after completing an appropriate training. Modifications to the EDC will be made if deemed necessary by the study sponsor.

IRT System

A validated and 21 CFR Part 11 compliant IRT system will be used for randomization. The IRT system will be integrated with the EDC system and undergo validation to confirm study-specific configuration and UAT testing prior to release. The validation, testing and release documentation for the IRT system will be maintained on file by the study sponsor. Data entry will be performed by site personnel after completing an appropriate training. Modifications to the IRT system will be made if deemed necessary by the study sponsor.

Data cleaning

The database will be subject to initial inspection for omitted data, gross data inconsistencies, and deviations. Any deficiencies or deviations will be reviewed, and any necessary action determined (e.g., data query, communication with the study center).

Intermittent data review will be performed, and any discovered errors will be reported to the study site using the electronic query process (as necessary). The study site will be expected to review and complete the query. The data cleaning cycle will be repeated until all data are considered clean.

Data back-up, confidentiality and security

Incremental data back-up will be performed on a regular basis by the EDC system vendor. All media will be stored in a secure location. Passwords will be issued to appropriate personnel to ensure confidentiality and protection of data.

18.2.7 Investigational device accountability

Sponsor will provide an appropriate number of the investigational devices to the study sites free of charge. The sites maintain the investigational devices in a locked, secure location. Only clinical investigators participating in the study will have access to the investigational device. Dispensing

of investigational device will be documented by authorized personnel. Each batch of the investigational device will be assigned a serial/lot number for tracking purposes.

Investigational devices received by the clinical site will be logged in by the site personnel on inventory logs and/or the EDC system. Final reconciliation will be completed at each site before or during site closure. Any unused inventory of the investigational device will be returned to the sponsor at the direction of the sponsor or at the close of the study. At the end of the study, overall study final device reconciliation will be completed internally by the sponsor.

18.3 Blinding

In order to avoid introduction of bias and maintain integrity of the study data, blinding to the randomized treatment assignment at Day 0 will be maintained until all subjects enrolled in Stage 1 and 2 have completed Week 12 assessments, and the study dataset has been locked for the primary efficacy analysis. The blinding rules for each role involved are set up a priori (i.e., before enrollment of the first subject) and are detailed in **Table 6**.

18.4 Unblinding

After locking the study dataset for the primary efficacy analysis, which will occur after the last subject enrolled in Stage 2 completes Week 12 assessments, treatment assignments will be made available to Co-PI Rheumatologists (**Table 6**). The Co-PI Rheumatologists may inform subjects about the treatment they were assigned at Day 0.

Before locking the study dataset for the primary efficacy analysis, unblinding of subjects and Co-PI Rheumatologists can occur only in exceptional circumstances when knowledge of the actual treatment is absolutely essential for further management of the subject. Investigators must discuss with the sponsor's Chief Medical Officer (CMO) if he/she believes that unblinding is necessary. The CMO will determine whether or not unblinding is necessary. The decision and rationale to unblind or continue to blind will be documented and presented for review by the DMC to ensure concurrence with the recommendation. Any concerns or questions raised by the DMC are to be addressed and documented. If unblinding is recommended and the DMC concurs, the CMO will authorize the Co-PI Rheumatologist's access to the subject's treatment assignment in IRT. The Co-PI Rheumatologist should not reveal the subject's treatment assignment to the sponsor, subject or anyone else on the study staff. Unblinding should not necessarily be a reason for study treatment discontinuation.

Table 6: Blinding Matrix

Role	Blinded for duration of clinical study	Unblinded once last enrolled subject completes Week 12	Blinding assessment at Week 4 and 12
Subject	Y	Y	Y
Investigational Sites Staff			
Co-PI Rheumatologist	Y	Y	Y

Co-PI Surgeon	Y	Y	N
Joint Evaluator	Y	Y	Y
Clinical Research Coordinators & Site Staff	Y	Y	N
Sponsor			
Sponsor's Representatives, except Unblinded Technician(s)	Y	Y	--
Unblinded Technician(s) [¥]	N	Y	--
Study Biostatisticians	Y	Y	--
DMC			
Independent Biostatistician [§]	N	Y	--
DMC Chairperson and Members	N	Y	--

Abbreviations: DMC, data monitoring committee; No, no; PI, principal investigator; Y, yes; --, not applicable.

[¥] Independent from the clinical operations. Has access to a password-protected database with the randomization scheme to be able to register each implanted MicroRegulator to a particular set of stimulation rules based on the subject's treatment assignment.

[§] Non-voting statistician reporting to DMC. Responsible for receiving blinded data exports, accessing randomization assignments, conducting unblinded analyses and preparing outputs for review during DMC closed sessions.

18.5 Investigator Responsibilities

18.5.1 General responsibilities

- Co-PI Rheumatologists and Co-PI Surgeons are responsible for ensuring that an investigation is conducted per the signed investigator statement (Investigator Agreement/Commitment), the study protocol, and applicable regulations for protecting the rights, safety, and welfare of study subjects under the investigator's care and for the control of devices under investigation.
- Co-PI Rheumatologist assures the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the study EDC and all required reports.
- Co-PI Rheumatologist obtains informed consent of each patient to whom the treatment is administered in accordance with provisions of 21 CFR Part 50 and ISO14155. In addition, Co-PI Surgeon shall obtain written surgical informed consent, if required by their institution.
- All Co-PIs are responsible for complying with all applicable IRB requirements under 21 CFR Part 56 and ISO14155.
- All Co-PIs are responsible for disclosure of financial obligations/conflict of interest to the sponsor in accordance with provisions of 21 CFR Part 54.
- All Co-PIs shall be trained on their responsibilities under 21 CFR 11, 50, 54, 56, 812 and ISO14155.
- To ensure proper execution of the study protocol, each Co-PI will identify a research coordinator for this study. Working with and under the oversight of the Co-PI, the research coordinator ensures that all study requirements are fulfilled.

- Each Co-PI will allow monitoring and auditing of their clinical investigation procedure(s) by the sponsor or designee.
- Each Co-PI will ensure timely acquisition and delivery of source documentation and redacted medical records required for adjudication and reporting of AEs by sponsor.

18.5.2 Disposition of the investigational study device

Co-PIs shall administer the investigational device only to subjects under the Co-PI's personal supervision. The Co-PIs shall not supply the investigational device to any person not authorized to receive it. Co-PIs or designees are required to maintain adequate records of the disposition of the investigational devices, including dates, quantity, and use by subjects. All unopened unused devices must be returned to the sponsor.

18.5.3 Maintenance of study records

Co-PIs are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each subject participating in the investigational plan (including information maintained electronically such as digital imaging) per 21 CFR 812. The investigator will also maintain original source documents from which study-related data are derived, which may include, but are not limited to:

- Clinic progress notes recording patient's medical history and medications
- Medical charts with operative reports and condition of patient upon discharge
- Medical records regarding AEs, and investigational device malfunctions and deficiencies, use errors (as applicable) including treatment and clinical outcome
- Results of diagnostic examinations
- Imaging records such as X-rays, MRI or CT scans and associated reports (hard copy and digital copy of images, as applicable/available)
- Printouts of source data generated by technical equipment (e.g., ECG, X-ray, MRI) must be filed with the subject's records
- Notes of phone calls and/or correspondence indicating study center's attempts to follow study patients at the required follow-up visits until their participation in the study is complete or terminated
- Records relating to subject deaths (e.g., death certificate, autopsy report)

Co-PIs shall retain records required to be maintained for a period of 2 years following the date a marketing application is approved for the device for the indication for which it is being investigated. If no application is to be filed, records shall be retained for 2 years after the investigation is discontinued. To avoid error, the study site should contact the study sponsor prior to the destruction of study records to ensure that they no longer need to be retained. In addition,

the sponsor should be contacted if a Co-PI plans to leave the study center, so that arrangements can be made for the handling or transfer of study subjects study records, or if the records are moved to be under the oversight of a different sponsor-approved investigator or to an off-site location.

18.5.4 Required documents from study sites

The study site will provide to sponsor the following documents:

- CV for the participating Co-PI Rheumatologists and Co-PI Surgeons, as well as Sub-Is, as applicable
- Current medical license for the participating Co-PIs and Sub-Is
- Investigator agreement/commitment for the Co-PIs and Sub-Is
- Financial disclosure form for the participating Co-PIs and Sub-Is
- Protocol acknowledgement form for Co-PIs
- IRB study approval letter
- IRB approved ICF
- Fully executed CTA

The study site will initiate enrollment of subjects after providing to sponsor the above listed documentation for Co-PI Rheumatologist and Co-PI Surgeon, completing a site initiation visit, and receiving from sponsor a written authorization to begin enrollment.

18.6 Protection of Subject Confidentiality

In all clinical studies, confidentiality of protected health information may be breached due to study-related activities beyond those of routine clinical care. This risk will be minimized by not collecting personally identifying information on CRFs or other study related documentation to be provided to the study sponsor. It is the sponsor's policy to redact any subject's personally identifying information from any documentation sent to the sponsor that inadvertently contains it.

At all times throughout the clinical investigation, confidentiality will be observed by all parties involved. All data shall be secured against unauthorized access. Privacy and confidentiality of information about each subject shall be preserved in the reports and in any publication. Each subject participating in this study will be assigned a unique identifier. All database forms and source documents sent to the sponsor will be tracked, evaluated, and stored using only this unique identifier.

Co-PI Rheumatologists will maintain confidential study subject lists identifying all enrolled subjects. The Co-PI Rheumatologists bear responsibility for keeping these lists current and confidential. These lists will not be provided to the study sponsor.

Monitors and auditors will have access to the study screening and enrollment logs and other personally identifying information of study subjects to ensure that data reported in the EDC corresponds to the person who signed the ICF and the information contained in the original source documents. Such personal identifying information may include, the subject's name, address, date of birth, gender, race, and medical record number.

The subject's name, medical record number or address will not be recorded in the monitor's visit report or the database. Demographic data that will be recorded include age, race, and gender.

Any source documents copied for monitoring purposes by the sponsor will be identified by using the assigned subject's unique identifier in an effort to protect subject confidentiality. All personally identifiable information will be redacted from source documents.

18.7 Study Suspension or Early Termination

The study can be discontinued at the discretion of the DMC, Co-PIs or study sponsor for reasons including the following:

- Occurrence of AE unknown to date in respect to their nature, severity, or duration, or the unexpected incidence of known AE;
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Insufficient recruitment of subjects;
- Investigational device presents an unreasonable and significant risk to subjects (the sponsor may terminate the study immediately);
- Persistent non-compliance with the study protocol;
- Persistent non-compliance with the applicable ethics committee or regulatory requirements; or
- Sponsor decision to terminate the study.

If the study is discontinued or suspended prematurely, the sponsor shall promptly inform all clinical investigators and study centers of the termination or suspension and the reason(s) for termination. IRB, regulatory authorities, and the subject's physicians may also need to be informed, if deemed necessary.

18.8 Site Closeout

At the site close-out visit or before, the monitor ensures all outstanding study documents are reconciled, the Co-PI's files are accurate and complete, reviews record retention requirements with the Co-PIs, makes a final accounting of all study supplies, and ensures that all applicable requirements are met for the study. Any specific observations and actions made at this visit shall be documented in the close-out visit report.

18.9 Quality Assurance and Supervision by Authorities

All documents and data shall be produced and maintained in such a way to assure control of documents and data to protect the subject's privacy as far as reasonably practicable. The sponsor and representatives of the FDA or other regulatory authorities are permitted to inspect the study documents (e.g., study protocol, CRFs, and original study-relevant medical records/files) as needed. All attempts will be made to preserve subject confidentiality.

The study centers are subject to audit by study sponsor personnel or designee for protocol adherence, accuracy of CRFs and compliance with applicable regulations. The sponsor will communicate to the sites any patterns of non-compliance. The sponsor will work with the sites to determine any necessary corrective action, as applicable. The sponsor will continue to monitor sites until compliance has been secured. If the site continues to display non-compliance, more serious action may be taken by the sponsor. The study protocol, data-recording procedures, data handling and study reports are subject to an independent clinical Quality Assurance audit by sponsor, its designee, or health authorities.

18.10 IRB Approved ICF and Protection of Study Subjects

An IRB must review and approve an ICF specific to this study. The sponsor will provide an example ICF. The site may modify this example ICF to meet specific requirements. However, the ICF must contain all of the elements required by sponsor and applicable regulations (21 CRF Part 50 and BS EN ISO 14155 14155), which will be verified by sponsor. IRB approved ICF and renewed approvals as appropriate will be maintained by the site for the duration of the study. The original, signed and dated ICF for each subject should be maintained by the site for monitoring.

Subjects will be informed both verbally and in writing using the ICF about the nature of the study, the anticipated risks and benefits involved and the discomfort to which they will be exposed. Subjects will be instructed about their right to discontinue their participation at any time without prejudice or jeopardy to future medical care. Each subject must sign the ICF prior to any screening procedures. A copy of the signed ICF will be provided to the subject.

18.11 IRB Approval

An IRB approval of the study protocol and ICF is required prior to study commencement under 21 CFR Part 56. Co-PI must also obtain renewal of IRB approvals throughout the duration of the

study. They are also responsible for fulfilling any conditions of approval imposed by the reviewing IRB, such as safety reporting. Co-PI will provide the study sponsor with copies of such approvals and reports.

18.12 Other Investigator Reports

All Co-PIs are responsible for notifying the sponsor about the following within the specified timeline:

Type of Notification	Timeline
Withdrawal of IRB approval	Verbal report within 24 hours of becoming aware followed by a written report within 5 working days
Informed consent not obtained	Verbal or written report within 24 hours of becoming aware

Notifications must identify subjects using the unique study identifier to protect subject's confidentiality.

18.13 Final Clinical Study Report

A final clinical study report (CSR) will be prepared by the study sponsor and provided to the FDA and reviewing IRBs, as needed.

18.14 Publication Policy

At the completion of the study, an abstract reporting the results will be prepared and may be presented at scientific meeting(s). A manuscript may also be prepared for publication in a peer-reviewed scientific journal. Co-authorship will be granted to the National Co-PIs and those site Co-PIs from the top enrolling sites. Consistent with "Recommendations for the Conduct, Reporting, and Publication of Scholarly Work in Medical Journals", every author should meet the following for authorship:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and
- Drafting the work or revising it critically for important intellectual content; and
- Final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

19 COVID-19 CONTINGENCY MEASURES

This section identifies contingency measures for the study procedures and various aspects of study management to address limitations to study site visits imposed by the COVID-19 pandemic in

accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (March 2020, updated on September 21, 2020).

19.1 Study Procedures During COVID-19

The implementation of contingency measures should be consistent with the protocol to the extent possible, and sponsor and clinical investigators should document the reason for any contingency measures implemented.

- **Informed consent and Screening**. The ICF may be sent to prospective subjects for review and discussed remotely via phone contact or virtual visit but it must be signed and dated during on-site visit prior to and on the same day as the protocol-required screening assessments to confirm initial eligibility and obtain baseline values (see Section **11.2.2**).

  In the event that new information requires a subject be re-consented, the updated ICF may be sent to the subject electronically or via mail for review and discussed remotely via phone contact or virtual visit. The consent form can be signed, scanned and returned electronically to the site, returned by mail using a prepaid envelope provided by the site, or returned in person.

  COVID-19 screening procedures that may be mandated by the clinical sites do not need to be entered into EDC. If a potential subject tests positive for COVID-19, the subject is considered screen failure. This subject may be consented and screened following treatment and full recovery (see Section **11.2.2**)

- **Follow-up through Week 12.** If COVID-19 restrictions or subject's health status prevent the subject from attending a protocol-required on-site visit at Week 4 or 8, those visits can be conducted remotely (see sections below). Only one, not both, of those visits may occur remotely. The protocol-required Day 0 and Week 12 visits shall be conducted on-site to ensure in-person RA disease activity assessments needed for randomization and maintain data quality and integrity for the primary and key secondary efficacy endpoints. If a subject completes the Day 0 and Week 12 visits out of window because of COVID-19, this will be reported as a protocol deviation with COVID-19 as a reason. The data from these late visits can be leveraged based on scientifically based rationale and clinical judgement.

- **Follow-up after Week 12.** If COVID-19 restrictions or subject's health status prevent the subject from attending any of the protocol-required on-site visits, those visits can be conducted remotely (see sections below). If a subject completes any of the visits out of window because of COVID-19, this will be reported as a protocol deviation with COVID-19 as a reason. The data from these late visits can be leveraged based on scientifically based rationale and clinical judgement.

- **Remote RA disease activity assessments**. The HAQ-DI, SGA and Subject's pain questionnaires can be sent to the subject's home and completed during a virtual visit with study staff. The subject will return the completed and initialed paper questionnaires using envelopes provided by the study site. The TJC28 and SJC28 can be conducted during the

same virtual visit. In this case, the Joint Evaluator will instruct the subject on how to perform a self-evaluation of each joint. The Joint Evaluator will complete the source document worksheet based on the subject's self-assessment. The Joint Evaluator will complete the EGA based on the results of the joint assessment and interview of the subject conducted remotely via telemedicine. Blood collection for hsCRP will be set as missing if it cannot be performed either at subject's home or designated facility using the study kits. The visit type will be recorded in the EDC.

- **Pregnancy test.** If the pregnancy test must be completed remotely, a test kit will be delivered to the subject's home. Once completed, the subject is instructed to photograph the result and send it to the study staff. The photograph will be placed in the subject binder.
- **SF-36 and EQ-5D-5L and Subject Satisfaction Questionnaire**. The study staff can mail the paper questionnaires to the subject's home for completion during a virtual study visit. The completed and initialed questionnaires can be returned to the site in person or using envelopes provided by the study site. The visit type will be recorded in the EDC.
- **Blood collection.** In the event the clinical site has COVID-19 provisions for offering home health services, blood collection for hsCRP, RF, ACPA, eGFR, CBC, hsCRP and inflammatory biomarkers may be performed at the subject's home using the sponsor-supplied sampling kits. Once collected, samples shall be prepared and shipped from the study site in accordance with the instruction manual from the central laboratory service provider. The blood collection for RF, ACPA, eGFR, CBC and hsCRP can be done at a local laboratory performing such tests routinely. The sites should inform the sponsor about such cases. If samples cannot be shipped to the central laboratory, analysis should be performed locally. The local analysis shall be documented as a protocol deviation due to COVID-19. Blood collection for inflammatory biomarker shall only be collected at the study site or at the subject's home. If this cannot be done, a protocol deviation shall be reported for the missing assessment.
- **Post-surgical clearance.** Wound healing by the treating surgeon investigator or designee with special attention to wound infections can be completed during a virtual visit and documented on the corresponding source worksheet.
- **Blinding assessments.** The paper questionnaires can be sent to the subject, Joint Evaluator and Co-PI Rheumatologist's homes and completed individually during a virtual visit with study staff. The completed and initialed questionnaires can be returned to the site in person or using envelopes provided by the study site. The visit type will be recorded in the EDC.
- **Reporting of any AEs**, device deficiencies and change in concomitant medications can be completed during virtual visit and documented in the EDC.
- **Concomitant medication and background therapy.** The use and timing of vaccination and immunomodulatory therapies in relation to COVID-19 vaccination shall be administered in subjects per the ACR's COVID-19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases (March 4, 2021 or latest).

19.2 Contingency Measures for Study Management

- **SIV training**. The required training (see Section 18.2.1) can be completed through web-based self-training or in person through video conferencing. The training must be documented.
- **Data monitoring.** In the event an in-person study site visit is not permissible, CRAs will perform remote monitoring. Remote monitoring will include remote source data verification and collection of essential documents. Remote performance of source data verification will require the rheumatology site research coordinator to redact, scan and upload certified copies of source documents to a secure, cloud-based portal. Redacted copies should be kept in the investigator's site master file with records of their communication to the monitor. Uploaded source documents will be accessed by site monitors for source verification with entries in EDC. Issues identified and their resolution will be tracked through annotations made in the same system. Discrepancies between source and EDC will be managed and documented through the EDC query resolution process. Once source data verification is complete, the CRA will securely destroy any copy made locally and provide a certificate of destruction to the trial site.
- **EMR.** Collection of essential documents may be completed using the same process. If local study site policies allow access to the site electronic medical record (EMR) system, the CRA should be provided with secure, read-only access, including all modules relevant for review. This access should be restricted to the records of only those patients who participate in the trial. A list of the monitors to whom remote access has been granted should be maintained. In order to prevent unauthorized access, access rights should be revoked once remote SDV tasks have been completed for the trial. The EMR system should have an audit trail and be able to log information on who accessed data and when. Remote access to the EMR should only be possible using a two-factor authentication. It should not be possible to make local copies of trial participants' health records. Users should be aware of the automatic creation of temporary files on their computer when reviewing trial participant data and should securely delete such files immediately after each source data verification session. Situations where CRAs were unable to access, or had delay monitoring of a clinical site shall be documented, including whether identification of deviations or GCP non-compliance was delayed due to postponed monitoring Findings and action items resulting from remote monitoring can be discussed with Co-PI and site coordinator via teleconference. Monitoring activities shall be documented per normal procedure.
- **Reporting of protocol deviations.** When a deviation is the result of a COVID-19 limitation, the deviation report shall include the specific limitation imposed by COVID-19 leading to the inability to comply with the protocol.
- **Investigational device dispensing and accountability**. Delivery of Energizer and/or Energizer charger from the study site to subject’s home is permitted. Items must be shipped in the original, sponsor-supplied packaging, and the site shall retain record of the shipment and its receipt with device accountability documentation. In the event a subject needs to

return Energizer and/or its charger, a sponsor-supplied return kit will be sent to the subject from the site with instructions and prepaid shipping. In all cases, requirements under FDA regulations for maintaining required investigational device storage conditions and investigational device accountability remain under rheumatology site.

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21 APPENDICES

Appendix A: Required Minimum Washout Period from Biologic and Targeted Synthetic DMARDs Prior to Implant Procedure

Drug Generic (Brand) Name	Dosing Interval & Route, If Several	Minimum Washout Period Relative to Last Dose Administered (days)
Abatacept (Orencia)	Weekly SC	14
	Monthly IV	30
Adalimumab (Humira)	-	21
Anakinra (Kineret)	-	2
Baricitinib (Olumiant)	-	2
Certolizumab (Cimzia)	Every 2 weeks	21
	Every 4 weeks	30
Etanercept (Enbrel)	-	14
Golimumab (Simponi)	Every 4 weeks SQ	30
	Every 8 weeks IV	60
Infliximab (Remicade)	Every 4 weeks	30
	Every 6 weeks	40
	Every 8 weeks	60
Rituximab (Rituxan)	-	120
Sarilumab (Kevzara)	-	28
Tocilizumab (Actemra)	IV	30
	SC	21
Tofacitinib (Xeljanz XR)	-	2
Upadacitinib (Rinvoq)	-	2

Abbreviations: IV, intravenous; SC, subcutaneous.
Sources: Goodman (2017), Kerrigan (2019), 3-5 x half-life per drug prescribing information.

Appendix B: FDA Drug Safety Communication (DSC) issued on 09/01/2021 about JAK inhibitor

FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions

Approved uses also being limited to certain patients

This information is an update to the FDA Drug Safety Communication issued on February 4, 2021. FDA also previously communicated about the safety clinical trial with Xeljanz, Xeljanz XR (tofacitinib) in February 2019 and July 2019.

X-XX-2021 FDA Drug Safety Communication

What safety concern is FDA announcing?

Based on a completed U.S. Food and Drug Administration (FDA) review of a large randomized safety clinical trial, we have concluded there is an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death with the arthritis and ulcerative colitis medicines Xeljanz and Xeljanz XR (tofacitinib). This trial compared Xeljanz with another type of medicine used to treat arthritis called tumor necrosis factor (TNF) blockers in patients with rheumatoid arthritis. The trial's final results also showed an increased risk of blood clots and death with the lower dose of Xeljanz. A prior DSC based upon earlier results from this trial, reported an increased risk of blood clots and death only seen at the higher dose.

We are requiring new and updated warnings for two other arthritis medicines in the same drug class as Xeljanz, called Janus kinase (JAK) inhibitors, Olumiant (baricitinib) and Rinvoq (upadacitinib). Olumiant and Rinvoq have not been studied in trials similar to the large safety clinical trial with Xeljanz, so the risks have not been adequately evaluated. However, since they share mechanisms of action with Xeljanz, FDA considers that these medicines may have similar risks as seen in the Xeljanz safety trial.

Two other JAK inhibitors, Jakafi (ruxolitinib) and Inrebic (fedratinib), are not indicated for the treatment of arthritis and other inflammatory conditions and so are not a part of the updates being required to the prescribing information for Xeljanz, Xeljanz XR, Olumiant, and Rinvoq. Jakafi and Inrebic are used to treat blood disorders and require different updates to their prescribing information. If FDA becomes aware of any additional safety information or data that warrants updates to the prescribing information for these medicines, we may take further action and will alert the public.

What is FDA doing?

We are requiring revisions to the *Boxed Warning*, FDA's most prominent warning, for Xeljanz/Xeljanz XR, Olumiant, and Rinvoq to include information about the risks of serious heart-related events, cancer, blood clots, and death. Recommendations for health care professionals will include consideration of the benefits and risks for the individual patient prior to initiating or continuing therapy. In addition, to ensure the benefits of these three medicines outweigh the risks in patients who receive them, we are limiting all approved uses to certain patients who have not responded or cannot tolerate one or more TNF blockers. Changes will also be made to several sections of the prescribing information and to the patient Medication Guide.

What are Xeljanz/Xeljanz XR, Olumiant, and Rinvoq and how can they help me?
Xeljanz/Xeljanz XR, Olumiant, and Rinvoq are used to treat certain serious, chronic, and progressive inflammatory conditions. Xeljanz was the first to be approved in 2012. All three medicines are approved to be used alone or with other drugs to treat rheumatoid arthritis (RA), a condition in which the body attacks its own joints, causing pain, swelling, joint damage, and loss of function. Xeljanz is also approved to treat psoriatic arthritis, a condition that causes joint pain and swelling; ulcerative colitis, which is a chronic, inflammatory disease affecting the colon; and polyarticular course juvenile idiopathic arthritis, a type of childhood arthritis. Xeljanz/Xeljanz XR, Olumiant, and Rinvoq work by decreasing the activity of the immune system; an overactive immune system contributes to RA, psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis.

What should patients do?
Those taking Xeljanz/Xeljanz XR, Olumiant, or Rinvoq should tell your health care professional if you are a current or past smoker, or have had a heart attack, other heart problems, stroke, or blood clots in the past as these may put you at higher risk for serious problems with the medicines. Patients starting these medicines should also tell your health care professional about these risk factors. Seek emergency help right away if you have any symptoms that may signal a heart attack, stroke, or blood clot, including:

- Discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
- Severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- Unusual pain or discomfort in your arms, back, neck, jaw, or stomach
- Shortness of breath with or without chest discomfort
- Breaking out in a cold sweat
- Nausea or vomiting
- Feeling lightheaded
- Weakness in one part or on one side of your body
- Slurred speech
- Drooping on one side of your mouth
- Swelling of a leg or arm
- Leg pain or tenderness, or red or discolored skin in the painful or swollen leg or arm

Treatment with these medicines is associated with an increased risk of certain cancers including lymphoma and lung cancer, so inform your health care professional if you experience signs and symptoms such as swelling of lymph nodes in your neck, armpits, or groin; constantly feeling tired; fever; night sweats; persistent or worsening cough; difficulty breathing; hoarseness or wheezing; or unexplained weight loss. Talk to your health care professional if you have any questions or concerns.

What should health care professionals do?
Health care professionals should consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Xeljanz/Xeljanz XR, Olumiant, or Rinvoq. This is particularly the case in patients who are current or past smokers, those with other cardiovascular risk factors, those who develop a malignancy, and those with a known malignancy other than a

successfully treated nonmelanoma skin cancer. Reserve these medicines for patients who have had an inadequate response or intolerance to one or more TNF blockers. Counsel patients about the benefits and risks of these medicines and advise them to seek emergency medical attention if they experience signs and symptoms of a heart attack, stroke, or blood clot.

What did FDA find?
When FDA first approved Xeljanz, we required the manufacturer, Pfizer, to conduct a safety clinical trial in patients with RA who were taking methotrexate to evaluate the risk of serious heart-related events, cancer, and infections. The trial studied two doses of Xeljanz (5 mg twice daily, which is the approved dosage for RA, and a higher 10 mg twice daily dosage) in comparison to a TNF blocker also used to treat the condition. Patients in the trial were required to be at least 50 years old and have at least one risk factor for heart disease.

Our review of the final trial results showed a higher rate of serious heart-related events such as heart attack and stroke, cancer, blood clots, and death in patients treated with both doses of Xeljanz compared to those treated with TNF blockers. Importantly, a higher rate of blood clots and death was seen with both doses of Xeljanz compared to TNF blockers, whereas previous interim results showed the risk only with the higher dose. For cancers, a higher rate of lymphomas was observed in patients treated with Xeljanz compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with Xeljanz compared to those treated with TNF blockers. Current or past smokers had an additional increased risk of overall cancers (See Data Summary).

Other JAK inhibitors have not been studied in similar large safety clinical trials, so the risk with these medicines has not been evaluated. However, since they share mechanisms of action with Xeljanz, FDA considers that these medicines may have similar risks as seen in the safety trial with Xeljanz.

What is my risk?
All medicines have side effects even when used correctly as prescribed, but in general the benefits of taking a medicine outweigh these risks. It is important to know that people respond differently to all medicines depending on their health, other medicines they are taking, the diseases they have, genetic factors, and many other factors. As a result, we cannot determine how likely it is that someone will experience these side effects when taking Xeljanz/Xeljanz XR, Olumiant, or Rinvoq.

However, if you are a current or past smoker, or have had a heart attack, other heart problems, stroke, or blood clots in the past, you should tell your health care professional as these may put you at higher risk for serious problems with these medicines.

How do I report side effects from Xeljanz, Olumiant, or Rinvoq?
To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving Xeljanz/Xeljanz XR, Olumiant, Rinvoq, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

How can I get new safety information on medicines I'm prescribing or taking?

U.S. FOOD & DRUG ADMINISTRATION

You can sign up for email alerts about Drug Safety Communications on medicines or medical specialties of interest to you.

Facts about Xeljanz/Xeljanz XR (tofacitinib), Olumiant (baricitinib), and Rinvoq (upadacitinib)

- These medicines are part of a class called Janus kinase (JAK) inhibitors and are used to treat certain serious, chronic, and progressive inflammatory conditions.
- All three medicines are approved to be used alone or with other medicines to treat rheumatoid arthritis. Xeljanz is also approved to treat psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis.
- These medicines work by decreasing the activity of the immune system.
- These medicines are available to be given orally as immediate-release tablets, extended-release tablets that release the medicine into the body over time, and solution.
- Common side effects of these medicines include upper respiratory tract infections such as the common cold and sinus infections, bronchitis, headache, cough, increased cholesterol levels, high blood pressure, increased muscle enzyme levels, rash, nausea, diarrhea, acne, cold sores, and shingles.

Additional Information for Patients

- FDA is requiring new and updated warnings about an increased risk of serious heart-related events such as heart attack or stroke , cancer, blood clots, and death with the medicines Xeljanz/Xeljanz XR (tofacitinib), Olumiant (baricitinib), and Rinvoq (upadacitinib) used to treat certain serious inflammatory conditions including rheumatoid arthritis (RA) and ulcerative colitis.
- We are also limiting the use of these medicines to certain patients who are not treated effectively or who experience severe side effects with another type of medicine used to treat serious inflammatory conditions called tumor necrosis factor (TNF) blockers.
- If you are taking Xeljanz/Xeljanz XR, Olumiant, or Rinvoq, tell your health care professional if you are a current or past smoker, or have had a heart attack, other heart problems, stroke, or blood clots in the past as these may put you at higher risk for serious problems with the medicines. Before starting these medicines, also tell your health care professional about these risk factors.
- Seek emergency help right away if you have any symptoms that may signal a heart attack, stroke, or blood clot, including:
    - Discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
    - Severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
    - Pain or discomfort in your arms, back, neck, jaw, or stomach
    - Shortness of breath with or without chest discomfort
    - Breaking out in a cold sweat
    - Nausea or vomiting
    - Feeling lightheaded
    - Weakness in one part or on one side of your body
    - Slurred speech

- Drooping on one side of your mouth
- Swelling of a leg or arm
- Leg pain or tenderness, or red or discolored skin in the painful or swollen leg or arm

- Also inform your health care professionals if you experience signs and symptoms such as:
  - Swelling of lymph nodes in your neck, armpits or groin
  - Constantly feeling tired
  - Fever
  - Night sweats
  - Persistent or worsening cough
  - Difficulty breathing
  - Hoarseness or wheezing
  - Unexplained weight loss.
- Read the patient Medication Guide every time you receive a prescription for Xeljanz/Xeljanz XR, Olumiant, or Rinvoq. The Medication Guide will be updated with this new or other important information about your medicine. It explains the important things that you need to know. These include the side effects, what the medicine is used for, how to take and store it properly, and other things to watch out for when you are taking the medicine.
- Talk to your health care professional if you have any questions or concerns.
- To help FDA track safety issues with medicines, report side effects from Xeljanz, Olumiant, Rinvoq, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.
- You can sign up for email alerts about Drug Safety Communications on medicines or medical specialties of interest to you.

Additional Information for Health Care Professionals

- FDA is requiring new and updated warnings about an increased risk of major adverse cardiovascular events, malignancy, thrombosis, and mortality with the Janus kinase (JAK) inhibitors Xeljanz, Xeljanz XR (tofacitinib), Olumiant (baricitinib), and Rinvoq (upadacitinib).
- Reserve these medicines for patients who have had an inadequate response or intolerance to one or more TNF blockers.
- Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Xeljanz/Xeljanz XR, Olumiant, or Rinvoq, particularly in patients who are current or past smokers, those with other cardiovascular risk factors, those who develop a malignancy, and those with a known malignancy other than a successfully treated nonmelanoma skin cancer.
- Inform patients about the symptoms of serious cardiovascular events and to seek emergency medical attention if they occur.
- Encourage patients to read the Medication Guide they receive with each prescription, which explains the safety risks and provides other important information.
- To help FDA track safety issues with medicines, report adverse events involving Xeljanz/Xeljanz XR, Olumiant, Rinvoq, or other medicines to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of this page.
- You can sign up for email alerts about Drug Safety Communications on medicines or medical specialties of interest to you.

Data Summary

When FDA first approved Xeljanz (tofacitinib), we required the manufacturer, Pfizer, to conduct a randomized safety clinical trial in patients with rheumatoid arthritis (RA) who were taking methotrexate to evaluate the risk of cardiovascular events, malignancy, and infections. It was a multicenter, randomized, open-label trial to evaluate two doses of Xeljanz (5 mg twice daily (N=1455), which is the approved dosage for RA, and a higher 10 mg twice daily dosage (N=1456)) in comparison to treatment with a tumor necrosis factor (TNF) blocker (N=1451). Patients in the trial were required to be 50 years of age or older and have at least one cardiovascular risk factor. The co-primary endpoints were major adverse cardiovascular events (MACE), defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; and malignancy, excluding nonmelanoma skin cancer (NMSC). The trial was designed to exclude a prespecified risk margin of 1.8 for the hazard ratio of combined Xeljanz regimens when compared to the TNF blocker control for each co-primary endpoint. The median on-study follow-up time was 4 years.

The mean age of the population was 61 years and the median age was 60 (range 50-88 years). Most patients were female (78 percent) and Caucasian (77 percent). The noninferiority criterion was not met for the comparison of the combined Xeljanz regimens to TNF blockers for the endpoints of MACE and malignancies since the upper limit of the 95% confidence intervals (CI) for these hazard ratios exceeded the prespecified noninferiority criterion of 1.8. For MACE, the estimated hazard ratio and 95% CI associated with the combined Xeljanz regimens relative to TNF blockers were 1.33 (0.91, 1.94). For malignancies excluding NMSC, the estimated hazard ratio and 95% CI associated with the combined Xeljanz regimens relative to TNF blockers were 1.48 (1.04, 2.09).

There was an increased risk of death, MACE, malignancies, and thrombosis associated with both regimens of Xeljanz. The data showed evidence of a dose-dependent increased risk for MACE, all-cause mortality, and thrombosis at both doses of Xeljanz when compared to treatment with TNF blockers. Additionally, the data showed evidence of a non-dose-dependent increased risk for malignancy excluding NMSC at both doses of Xeljanz when compared to TNF blockers. Lymphomas and lung cancers were observed at a higher rate in patients treated at both doses of Xeljanz compared to those treated with TNF blockers. In particular, a higher rate of lung cancers was observed in current or past smokers treated with Xeljanz. Current or past smokers had an additional increased risk of overall cancers.

Other JAK inhibitors have not been studied in similar large safety clinical trials, so the risk with these medicines has not been evaluated. However, since they share mechanisms of action with Xeljanz, FDA considers that these medicines may have similar risks as seen in the safety clinical trial with Xeljanz.

Related Information

National Institute of Arthritis and Musculoskeletal and Skin Diseases: Rheumatoid Arthritis

National Institute of Arthritis and Musculoskeletal and Skin Diseases: Psoriatic Arthritis

National Institute of Diabetes and Digestive and Kidney Diseases: Ulcerative Colitis

Genetic and Rare Diseases Information Center: Polyarticular onset juvenile idiopathic arthritis

National Heart, Lung, and Blood Institute: Heart Attack

National Heart, Lung, and Blood Institute: Stroke

National Heart, Lung, and Blood Institute: Venous Thromboembolism

National Cancer Institute

FDA: Information on Tumor Necrosis Factor (TNF) Blockers

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

Think It Through: Managing the Benefits and Risks of Medicines