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Supplementary information

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Vagus nerve-mediated neuroimmune modulation for rheumatoid arthritis: a pivotal randomized controlled trial

In the format provided by the authors and unedited

Supplementary Appendix – online supplement

RESET-RA Trial (Clinicaltrials.gov number, NCT04539964)

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Abbreviation: AE, adverse event

**NOTE: Tables S17- S20 report AEs during long-term follow-up through database lock of March 10, 2025 (i.e. all available safety data at time of database lock, not limited to 12 months, with mean implant duration of >700 days).*

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Section 3: INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

Subjects eligible for enrollment in the study met *all* 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. 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. *Note:* Enrollment of subjects with inadequate response or loss of response to JAKi was limited to 6 subjects.
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 were:
    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 were allowed if indicated by the treating physician. Lower stable doses were allowed if dose limiting toxicity precluded use of a higher dose. Combinations were allowed provided all drugs comprising the combination meet stability requirements.
6. Willing and able to comply with protocol requirements.

Exclusion Criteria

Subjects eligible for enrollment met 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.
2. Demonstrated an inadequate response or loss of response to JAKi, once 6 subjects meeting this criterion were 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 was permissible.
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 Charger (formerly known as Energizer).
33. Requires treatment by any of the prohibited interventions.
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.
46.

Section 4: DESCRIPTION OF EFFICACY ENDPOINTS

Primary Endpoint

The ACR20 is the most common primary endpoint in randomized controlled trials (RCTs) to evaluate treatment in RA. The FDA considers ACR20 a well-validated composite endpoint for assessing the signs and symptoms of RA, as noted in guidance provided to industry on the conduct of trials in patients with RA.

ACR20 response criteria continues to be an accepted measure to demonstrate reduction in RA disease activity. ACR20 is a dichotomous composite endpoint indicating the proportion of patients with at least 20 percent improvement in the number of tender and swollen joints, and in three out of the remaining five ACR core-set measures: subject pain, subject global assessment of disease, evaluator global assessment of disease, physical functioning assessment (Health Assessment Questionnaire-Disability Index [HAQ-DI]), and acute phase reactants (i.e., hsCRP).

The core set of measures included in the ACR response criteria was established through a consensus process of clinical experts. Individual criteria were selected based on their construct validity, face validity, content validity, criterion validity, and discriminant

validity. When considering the ability of an outcome measure to detect change, pain assessments, global assessments, tender joint counts, and HAQ scores all had strong discriminant validity.[1]

Key Secondary Endpoints

ACR20 response from Day 0

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

DAS28-CRP response (MCID)

The DAS28-CRP is a validated measure for assessing disease activity in RA.[2]

The DAS28-CRP score is a composite index providing a measure of disease activity, comprising TJC28, SJC28, SGA, and 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*

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

DAS28-CRP good/moderate EULAR response

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

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

[1] van Riel PL, van Gestel AM. Clinical outcome measures in rheumatoid arthritis. Ann Rheum Dis. 2000;59 Suppl 1:i28–i31.
[2] Wells G, Becker JC, Teng J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009;68(6):954–960.

EULAR Response Criteria

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

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

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

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

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

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

There is a high level of agreement between ACR and EULAR improvement classification, and their validity is equivalent. The discriminating potential of the criteria between treatment groups is comparable.[3]

HAQ-DI response (MCID)

The HAQ–Disability Index (HAQ-DI) is a comprehensive measure of the patient's perception of functional status and has been widely validated in RA.[4] Subjects completed the HAQ-DI questionnaire using a validated paper form in their language (English or Spanish). There are 20 questions in eight categories to assess a patient's physical functional status: dressing, arising, eating, walking, hygiene, reach, grip, and common activities. Each functional area contains at least 2 questions. For each question, there is a 4-level response set that is scored from 0 (without any difficulty) to 3 (unable to do). If aids or devices or physical assistance are used for a specific functional area, and the maximum response of this functional area is 0 or 1, the according value is increased to a score of 2. The highest

[3] van Gestel AM, Anderson JJ, van Riel PL, et al. ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. J Rheumatol. 1999;26(3):705–711.
[4] Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23(2):137–145.

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

Additional Endpoints

DAS28-CRP score change, LDA/remission

The Disease Activity Score (DAS) is a derived measurement of 4 components with differential weighting:

- TJC28
- SJC28
- hsCRP (mg/L)
- SGA

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

If one of the components was missing at an individual assessment point, the DAS28-CRP value for that assessment was set to missing.

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

- 0 to < 2.6 Remission
- 2.6 to < 3.2 Low disease activity (LDA)
- 3.2 to ≤ 5.1 Moderate activity

[5] Linde L, Sorensen J, Ostergaard M, Horslev-Petersen K, Hetland ML. Health-related quality of life: validity, reliability, and responsiveness of SF-36, 15D, EQ-5D RAQoL, and HAQ in patients with rheumatoid arthritis. J Rheumatol. 2008;35(8):1528–1537.

[6] V. Strand, A. Balbir-Gurman, K. Pavelka, P. Emery, N. Li, M. Yin, P. B. Lehane, S. Agarwal, Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years, *Rheumatology*, Volume 45, Issue 12, December 2006, Pages 1505–1513, https://doi.org/10.1093/rheumatology/kel358

- > 5.1 High activity

If one of the components was missing at a given assessment point, no imputations were done, and the DAS28-CRP value for that assessment was set to missing.

CDAI score change, LDA/remission, response

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.

CDAI is easy to apply, sensitive to change, and correlates with the two main outcomes of RA: disability and damage. The ACR/EULAR index-based remission definition uses CDAI and early improvement correlates with good outcomes.[7,8]

[7] Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol. 2005;23(5 Suppl 39):S100–108.
[8] Gaujoux-Viala C, Mouterde G, Baillet A, et al. Evaluating disease activity in rheumatoid arthritis: which composite index is best? A systematic literature analysis of studies comparing the psychometric properties of the DAS, DAS28, SDAI and CDAI. Joint Bone Spine. 2012;79(2):149–155.

Section 5: AUGMENTED THERAPY - DEFINITION

Per Statistical Analysis Plan during open-label, extended follow-up, subjects combining stimulation with the following additions to RA therapy will fall into the augmented therapy subgroup for analysis, with augmented therapy defined as:

- *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.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Table S1 - Baseline Demographics of Patients in RESET-RA Study			
	Arm 1 (N=122)	**Arm 2 (N=120)**	**All (N=242)**
Age (years)			
Mean (SD)	55.8 (10.3)	55.5 (10.5)	55.7 (10.4)
Median	57.0	56.5	57.0
Min, Max	25, 75	30, 75	25, 75
Gender			
Male	24 (19.7%)	10 (8.3%)	34 (14.0%)
Female	98 (80.3%)	110 (91.7%)	208 (86.0%)
Ethnicity			
Hispanic or Latino	23 (18.9%)	22 (18.3%)	45 (18.6%)
Not Hispanic or Latino	98 (80.3%)	95 (79.2%)	193 (79.8%)
Not disclosed	1 (0.8%)	3 (2.5%)	4 (1.7%)
Race [1]			
American Indian or Alaska Native	1 (0.8%)	0 (0.0%)	1 (0.4%)
Asian	4 (3.3%)	5 (4.2%)	9 (3.7%)
Black or African American	10 (8.2%)	12 (10.0%)	22 (9.1%)
Native Hawaiian or other Pacific Islander	0 (0.0%)	1 (0.8%)	1 (0.4%)
White	102 (83.6%)	93 (77.5%)	195 (80.6%)
Other	5 (4.1%)	9 (7.5%)	14 (5.8%)
BMI (kg/m^2)			
Mean (SD)	30.7 (7.3)	29.8 (6.7)	30.3 (7.0)
Median	29.6	28.7	29.2
Min, Max	18.9, 56.7	17.9, 54.1	17.9, 56.7
[1] Race reported as “Other” if more than 1 race is selected			

Table S2 - Baseline Prior b/tsDMARD History			
	Arm 1 (N=122)	**Arm 2 (N=120)**	**All (N=242)**
Prior b/tsDMARDs			
Mean (SD)	2.5 (2.0)	2.7 (1.9)	2.6 (1.9)
Median	2.0	2.0	2.0
Min, Max	1.0, 12.0	1.0, 10.0	1.0, 12.0
Number of prior b/tsDMARDs			
0	0	0	0
1	52 (42.6%)	42 (35.0%)	94 (38.8%)
2	25 (20.5%)	28 (23.3%)	53 (21.9%)
3 or more (3+)	45 (36.9%)	50 (41.7%)	95 (39.3%)

Table S2 - Baseline Prior b/tsDMARD History			
	Arm 1 (N=122)	**Arm 2 (N=120)**	**All (N=242)**
Prior b/tsDMARD by Classification			
Anti-IL-1 agents	0 (0.0%)	4 (3.3%)	4 (1.7%)
Anti-IL-6 agents	27 (22.1%)	28 (23.3%)	55 (22.7%)
Anti-TNF agents	116 (95.1%)	109 (90.8%)	225 (93.0%)
B-cell depleting agents	13 (10.7%)	21 (17.5%)	34 (14.0%)
JAKi	25 (20.5%)	24 (20.0%)	49 (20.2%)
CTLA4-Ig	32 (26.2%)	36 (30.0%)	68 (28.1%)

Abbreviations: CTLA4-Ig, cytotoxic T-lymphocyte-associated antigen-4 immunoglobulin; IL, interleukin; JAKi, Janus kinase inhibitor; SD, standard deviation; TNF, tumor necrosis factor

Table S3 - Baseline Scores for Disease Activity and ACR Response Rate Components			
	Arm 1 (N=122)	**Arm 2 (N=120)**	**All (N=242)**
RA duration (years)			
Mean (SD)	13.0 (10.6)	11.8 (10.4)	12.4 (10.5)
Median	10.0	8.5	9.2
Min, Max	0.1, 55.5	0.7, 51.8	0.1, 55.5
CDAI score			
Mean (SD)	36.1 (12.6)	38.2 (12.8)	37.1 (12.7)
Median	33.8	37.1	35.1
Min, Max	13.5, 73.5	16.5, 74.0	13.5, 74.0
DAS28-CRP score			
Mean (SD)	5.3 (0.91)	5.4 (0.96)	5.3 (0.93)
Median	5.2	5.3	5.3
Min, Max	3.4, 7.6	3.0, 7.9	3.0, 7.9
Serology			
Negative	56 (45.9%)	54 (45.0%)	110 (45.5%)
Positive	62 (50.8%)	66 (55.0%)	128 (52.9%)
Not Done	4 (3.3%)	0 (0.0%)	4 (1.7%)
TJC28			
Mean (SD)	14.1 (6.9)	15.0 (7.3)	14.6 (7.1)
Median	12.4	14.0	14.0
Min, Max	4.0, 28.0	4.0, 28.0	4.0, 28.0
SJC28			
Mean (SD)	9.6 (5.5)	10.5 (5.0)	10.0 (5.2)
Median	7.8	9.2	9.0
Min, Max	4.0, 28.0	4.0, 28.0	4.0, 28.0
HAQ-DI score			
Mean (SD)	1.4 (0.6)	1.3 (0.6)	1.4 (0.6)

Table S3 - Baseline Scores for Disease Activity and ACR Response Rate Components			
	Arm 1 (N=122)	**Arm 2 (N=120)**	**All (N=242)**
Median	1.4	1.4	1.4
Min, Max	0.1, 2.8	0.0, 2.9	0.0, 2.9
Pain (per patient report)			
Mean (SD)	5.5 (2.0)	5.7 (2.2)	5.6 (2.1)
Median	5.5	6.0	6.0
Min, Max	1.0, 10.0	1.0, 10.0	1.0, 10.0
Patient Global Assessment			
Mean (SD)	6.2 (2.1)	6.0 (2.3)	6.1 (2.2)
Median	6.0	6.0	6.0
Min, Max	2.0, 10.0	1.0, 10.0	1.0, 10.0
Physician Global Assessment			
Mean (SD)	6.3 (1.9)	6.7 (1.7)	6.5 (1.8)
Median	6.3	7.0	7.0
Min, Max	1.5, 10.0	2.0, 10.0	1.5, 10.0
hsCRP (mg/L)			
Mean (SD)	8.41 (12.34)	8.01 (12.76)	8.21 (12.53)
Median	3.87	2.63	3.08
Min, Max	0.15, 69.76	0.09, 85.48	0.09, 85.48

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

BLINDING

Bang's blinding index: An *ad-hoc* cut-off of 0.2 to 0.3 has been reported in the literature as indicative of successful blinding.[9]

Table S4: Blinding Summary at Week 4 & 12; ITT Population

Joint Evaluator						
Assignment	**Stimulation Strongly Believe**	**Stimulation Somewhat Believe**	**Sham Somewhat Believe**	**Sham Strongly Believe**	**Don't Know**	**BI (95% CI)**
Month 1						
Stimulation	33 (27.7%)	46 (38.7%)	22 (18.5%)	9 (7.6%)	9 (7.6%)	0.30 (0.21, 0.39)
Sham	15 (12.6%)	37 (31.1%)	26 (21.8%)	21 (17.6%)	20 (16.8%)	0.00 (-.11, 0.12)
Month 3						
Stimulation	35 (29.7%)	32 (27.1%)	19 (16.1%)	21 (17.8%)	11 (9.3%)	0.17 (0.07, 0.28)
Sham	20 (16.8%)	31 (26.1%)	25 (21.0%)	27 (22.7%)	16 (13.4%)	0.03 (-.09, 0.16)

Co-PI						
Assignment	**Stimulation Strongly Believe**	**Stimulation Somewhat Believe**	**Sham Somewhat Believe**	**Sham Strongly Believe**	**Don't Know**	**BI (95% CI)**
Month 1						
Stimulation	33 (28.4%)	44 (37.9%)	18 (15.5%)	6 (5.2%)	15 (12.9%)	0.34 (0.26, 0.43)
Sham	11 (9.8%)	30 (26.8%)	28 (25.0%)	25 (22.3%)	18 (16.1%)	0.12 (-.01, 0.24)
Month 3						
Stimulation	37 (30.8%)	36 (30.0%)	19 (15.8%)	18 (15.0%)	10 (8.3%)	0.23 (0.13, 0.33)
Sham	18 (15.5%)	28 (24.1%)	26 (22.4%)	38 (32.8%)	6 (5.2%)	0.16 (0.03, 0.30)

Patient						
Assignment	**Stimulation Strongly Believe**	**Stimulation Somewhat Believe**	**Sham Somewhat Believe**	**Sham Strongly Believe**	**Don't Know**	**BI (95% CI)**
Month 1						
Stimulation	45 (37.5%)	34 (28.3%)	13 (10.8%)	11 (9.2%)	17 (14.2%)	0.37 (0.28, 0.46)
Sham	18 (15.3%)	26 (22.0%)	16 (13.6%)	47 (39.8%)	11 (9.3%)	0.20 (0.06, 0.34)
Month 3						
Stimulation	48 (39.7%)	29 (24.0%)	10 (8.3%)	24 (19.8%)	10 (8.3%)	0.28 (0.17, 0.38)
Sham	24 (20.2%)	21 (17.6%)	10 (8.4%)	52 (43.7%)	12 (10.1%)	0.19 (0.04, 0.34)

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Table S5: Primary and Key Secondary Endpoints

Double-Blind, Controlled Period, 3 Months by ITT Analysis				
Primary Endpoint by no. of responders (%)				
	Arm 1: Stimulation (N=122)	**Arm 2: Sham (N=120)**	**Difference vs. Sham – percentage points (95% CI)**	**P-value for difference**
ACR20 from baseline	43 (35.2)	29 (24.2)	11.8 (0.6, 23.1)	0.0209
Secondary Endpoints by no. of responders (%)				
	Stimulation (N=122)	**Sham (N=120)**	**Difference vs. Sham –percentage points (95% CI)**	**P-value for difference, adjusted**
EULAR Good/Moderate	74 (60.7)	50 (41.7)	19.5 (7.3, 31.7)	0.0048
DAS28-CRP MCID	55 (45.1)	39 (32.5)	13.2 (1.1, 25.3)	0.0528
HAQ-DI MCID	56 (45.9)	44 (36.7)	9.0 (-3.3, 21.4)	0.0797
ACR20 from Day 0	38 (31.1)	27 (22.5)	8.0 (1.1, 25.3)	0.0797

Open-Label Stimulation, 6 Months, 9 Months, 12 Months by All Completer Analysis									
	6 Months			**9 Months**			**12 Months**		
Percentage of responders (n/N)									
	Arm 1	**Arm 2**	**All**	**Arm 1**	**Arm 2**	**All**	**Arm 1**	**Arm 2**	**All**
ACR20 from baseline (All completers)	44.5 (53/119)	55.6 (65/117)	50.0 (118/236)	47.9 (57/119)	55.6 (64/115)	51.7 (121/234)	51.3 (61/119)	54.4 (62/114)	52.8 (123/233)
ACR20 from baseline **(NRI for missing/withdrawn)**	43.8 (53/121)	54.2 (65/120)	49.0 (118/241)	47.1 (57/121)	53.3 (64/120)	50.2 (121/241)	50.4 (61/121)	51.7 (62/120)	51.0 (123/241)
EULAR Good/Moderate (All completers)	66.1 (78/118)	70.1 (82/117)	68.1 (160/235)	73.7 (84/114)	75.7 (81/107)	74.7 (165/221)	72.6 (85/117)	76.6 (85/111)	74.6 (170/228)
EULAR Good/Moderate (NRI for missing/withdrawn)	64.5 (78/121)	68.3 (82/120)	66.4 (160/241)	69.4 (84/121)	67.5 (81/120)	68.5 (165/241)	70.2 (85/121)	70.8 (85/120)	70.5 (170/241)
DAS28-CRP MCID (All completers)	53.4 (63/118)	59.8 (70/117)	56.6 (133/235)	58.8 (67/114)	62.6 (67/107)	60.6 (134/221)	62.4 (73/117)	60.4 (67/111)	61.4 (140/228)
DAS28-CRP MCID (NRI for missing/withdrawn)	52.1 (63/121)	58.3 (70/120)	55.2 (133/241)	55.4 (67/121)	55.8 (67/120)	55.6 (134/241)	60.3 (73/121)	55.8 (67/120)	58.1 (140/241)
HAQ-DI MCID (All completers)	53.8 (64/119)	61.5 (72/117)	57.6 (136/236)	57.6 (68/118)	58.3 (67/115)	57.9 (135/233)	55.5 (66/119)	59.3 (67/113)	57.3 (133/232)
HAQ-DI MCID	52.9	60.0	56.4	56.2	55.8	56.0	54.5	55.8	55.2

(NRI for missing/withdrawn)	(64/121)	(72/120)	(136/241)	(68/121)	(67/120)	(135/241)	(66/121)	(67/120)	(133/241)
ACR20 from Day 0 (All completers)	43.7 (52/119)	47.9 (56/117)	45.8 (108/236)	50.4 (60/119)	52.2 (60/115)	51.3 (120/234)	48.7 (58/119)	44.7 (51/114)	46.8 (109/233)
ACR20 from Day 0 (NRI for missing/withdrawn)	43.0 (52/121)	46.7 (56/120)	44.8 (108/241)	49.6 (60/121)	50.0 (60/120)	49.8 (120/241)	47.9 (58/121)	42.5 (51/120)	45.2 (109/241)

Trial was not powered for the key secondary endpoints. The data trends in favor of stimulation when compared with sham during the sham-control, blinded period. The p-values were according to prespecified Hochberg procedure in the statistical analysis plan (SAP). NOTE: Baseline assessed on day consent, Day 0 (day of randomization); patient imputed as non-responder if rescued with medication prior to Week 12, regardless of treatment assignment; patient imputed as non-responder if missing at Week 12.

Table S6: Clinical Composite Outcome Measures, 3 Months through 12 Months

Double-Blind, Controlled Period, 3 Month by ITT Analysis – No. of Responders (%)

	Arm 1: Stimulation (N=122)	Arm 2: Sham (N=120)	Difference vs. Sham – percentage points (95% CI)	P-value for difference
ACR20 from baseline	43 (35.2)	29 (24.2)	11.8 (0.6, 23.1)	0.0209
EULAR Good/Moderate	74 (60.7)	50 (41.7)	19.5 (7.3, 31.7)	0.0048
DAS28-CRP LDA/Remission	31 (26.1)	18 (15.4)	11.4 (1.2-21.6)	0.0154
CDAI LDA/Remission	28 (23.3)	19 (16.0)	7.8 (-2.1-17.7)	0.0648

Open-Label Stimulation Period by All Completer Analysis – Percentage of Responders (n/N)

	6 Month			9 Month			12 Month		
	Arm 1	Arm 2	All	Arm 1	Arm 2	All	Arm 1	Arm 2	All
ACR20 from baseline	44.5 (53/119)	55.6 (65/117)	50.0 (118/236)	47.9 (57/119)	55.6 (64/115)	51.7 (121/234)	51.3 (61/119)	54.4 (62/114)	52.8 (123/233)

EULAR Good/Moderate	66.1 (78/118)	70.1 (82/117)	68.1 (160/235)	73.7 (84/114)	75.7 (81/107)	74.7 (165/221)	72.6 (85/117)	76.6 (85/111)	74.6 (170/228)
DAS28-CRP LDA/Remission (All completers)	30.5 (36/118)	31.6 (37/117)	31.1 (73/235)	33.3 (38/114)	37.4 (40/107)	35.3 (78/221)	42.7 (50/117)	37.8 (42/111)	40.3 (92/228)
DAS28-CRP LDA/Remission (NRI for missing/withdrawn)	29.8 (36/121)	30.8 (37/120)	30.3 (73/241)	31.4 (38/121)	33.3 (40/120)	32.4 (78/241)	41.3 (50/121)	35.0 (42/120)	38.2 (92/241)
CDAI LDA/Remission (All completers)	27.7 (33/119)	30.8 (36/117)	29.2 (69/236)	33.3 (39/117)	35.1 (40/114)	34.2 (79/231)	39.8 (47/118)	36.0 (41/114)	37.9 (88/232)
CDAI LDA/Remission (NRI for missing/withdrawn)	27.3 (33/121)	30.0 (36/120)	28.6 (69/241)	32.2 (39/121)	33.3 (40/120)	32.8 (79/241)	38.8 (47/121)	34.2 (41/120)	36.5 (88/241)

Open-Label Stimulation Period by Non-Augmented Analysis – Percentage of Responders (n/N)

	6 Month			**9 Month**			**12 Month**		
	Arm 1	**Arm 2**	**All**	**Arm 1**	**Arm 2**	**All**	**Arm 1**	**Arm 2**	**All**
ACR20 from baseline	51.5 (50/97)	53.1 (52/98)	52.6 (102/194)	51.7 (46/89)	62.1 (54/87)	56.8 (100/176)	55.8 (43/77)	59.3 (48/81)	57.6 (91/158)
EULAR Good/Moderate	73.7 (70/95)	70.4 (69/98)	72.0 (139/193)	75.3 (64/85)	78.0 (64/82)	76.6 (128/167)	77.3 (58/75)	77.2 (61/79)	77.3 (119/154)
DAS28-CRP LDA/Remission	36.8 (35/95)	32.6 (32/98)	34.7 (67/193)	36.5 (31/85)	42.7 (35/82)	39.5 (66/167)	49.3 (37/75)	40.5 (32/79)	44.8 (69/154)
CDAI LDA/Remission	34.4 (33/96)	31.6 (31/98)	33.0 (64/194)	39.1 (34/87)	40.2 (35/87)	39.7 (69/174)	47.4 (36/76)	40.7 (33/81)	43.9 (69/157)

Table S7: Mean Change in Tender Joint Count (TJC)

TJC Study Week	Arm 1: Stimulation (N=122) to Open-label Stimulation(N=121)				Arm 2: Sham (N=120) to Open-label Stimulation (N=120)				All (N=241)			
	n	Mean change	SD	SE	n	Mean change	SD	SE	n	Mean change	SD	SE
Month 3	116	-6.3*	8.15	0.76	114	-4.3	9.2	0.86	--	--	--	--
Long-term Follow-up, All completers												
Month 6	119	-7.4	7.63	0.70	117	-7.9	9.26	0.86	236	-7.6	8.46	0.55
Month 9	118	-7.6	7.99	0.74	114	-8.8	8.98	0.84	232	-8.2	8.50	0.56
Month 12	119	-7.9	8.28	0.76	114	-8.0	9.12	0.85	233	-7.9	8.70	0.57
Long-term Follow-up, Non-augmented												
Month 6	96	-8.2	7.75	0.79	98	-8.1	9.42	0.95	194	-8.1	8.61	0.62
Month 9	88	-7.4	7.62	0.81	87	-9.9	8.94	0.96	175	-8.6	8.37	0.63
Month 12	77	-8.3	7.82	0.89	80	-9.0	9.24	1.03	157	-8.7	8.55	0.68

*The difference in mean change between stimulation and sham was statistically significant by mixed-effect model repeated measures; P = 0.0014
Missing values of continuous endpoints were excluded from analysis.

Table S8: Mean Change in Swollen Joint Count (SJC)

SJC Study Week	Arm 1: Stimulation (N=122) to Open-label Stimulation(N=121)				Arm 2: Sham (N=120) to Open-label Stimulation (N=120)				All (N=241)			
	n	Mean change	SD	SE	n	Mean change	SD	SE	n	Mean change	SD	SE
Month 3	116	-4.4*	5.99	0.56	114	-3.3	5.59	0.52	--	--	--	--
Long-term Follow-up, All completers												
Month 6	119	-5.4	6.35	0.58	117	-5.7	5.93	0.55	236	-5.5	6.14	0.40
Month 9	118	-5.7	6.03	0.56	114	-6.3	6.27	0.59	232	-6.0	6.14	0.40
Month 12	119	-5.2	7.07	0.65	114	-6.5	5.88	0.55	233	-5.8	6.53	0.43
Long-term Follow-up, Non-augmented												
Month 6	96	-5.7	6.23	0.64	98	-5.5	5.82	0.59	194	-5.6	6.02	0.43
Month 9	88	-5.6	5.31	0.57	87	-6.7	6.19	0.66	175	-6.1	5.77	0.44
Month 12	77	-5.9	6.14	0.70	80	-6.7	5.76	0.64	157	-6.3	5.94	0.47

*The difference in mean change between stimulation and sham was statistically significant by mixed-effect model repeated measures; P = 0.0131
Missing values of continuous endpoints were excluded from analysis.

Table S9: Mean Change in DAS28-CRP Score

DAS28-CRP Study Week	Arm 1: Stimulation (N=122) to Open-label Stimulation(N=121)				Arm 2: Sham (N=120) to Open-label Stimulation (N=120)				All (N=241)			
	n	Mean change	SD	SE	n	Mean change	SD	SE	n	Mean change	SD	SE
Month 3	115	-1.1*	1.31	0.12	114	-0.7	1.28	0.12	--	--	--	--
Long-term Follow-up, All completers												
Month 6	118	-1.4	1.28	0.12	117	-1.4	1.44	0.13	235	-1.4	1.36	0.09
Month 9	114	-1.5	1.27	0.12	107	-1.6	1.39	0.13	221	-1.6	1.33	0.09
Month 12	117	-1.6	1.45	0.13	111	-1.7	1.45	0.14	228	-1.6	1.45	0.10
Long-term Follow-up, Non-augmented												
Month 6	95	-1.5	1.30	0.13	98	-1.4	1.43	0.14	193	-1.5	1.36	0.09
Month 9	85	-1.5	1.31	0.14	82	-1.7	1.39	0.15	167	-1.6	1.35	0.10
Month 12	75	-1.7	1.44	0.17	78	-1.7	1.45	0.16	153	-1.7	1.44	0.12

*The difference in mean change between stimulation and sham was statistically significant by mixed-effect model repeated measures; P = 0.0033

PATIENT SATISFACTION AND RECOMMENDATION

was assessed at 6 months using five-point Likert rating scale. Additionally, patients were asked a question about whether they would recommend the SetPoint System to family and friends.

Table S10: Patient Satisfaction and Recommendation at 6 Months

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

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

Table S11: Summary of Adverse Events from Screening to 3 Months

AE Category	Arm 1: Stimulation (N=122)		Arm 2: Sham (N=120)		All (N=243)	
	Events	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)
Any non-serious AE	207	78 (63.9%)	191	86 (71.7%)	398	164 (67.5%)
Unrelated [1]	160	67 (54.9%)	158	76 (63.3%)	318	143 (58.8%)
Related [2], [4]	37	25 (20.5%)	29	22 (18.3%)	66	47 (19.3%)
Implant Device	4	3 (2.5%)	7	4 (3.3%)	11	7 (2.9%)
Implant Procedure	23	16 (13.1%)	29	22 (18.3)	52	38 (15.6%)
Explant Procedure	2	1 (0.8%)	0	0	2	1 (0.4%)
Charger	1	1 (0.8%)	0	0	1	1 (0.4%)
Stimulation Therapy	11	10 (8.2)	0	0	11	10 (4.1%)
Indeterminate [3]	10	7 (5.7%)	4	4 (3.3%)	14	11 (4.5%)
Any SAE	5	4 (3.3%)	7	5 (4.2%)	12	9 (3.7%)
Unelated [1]	2	2 (1.6%)	6	4 (3.3%)	8	6 (2.5%)
Related [2], [4]	3	3 (2.5%)	1	1 (0.8%)	4	4 (1.6%)
Implant Device	1	1 (0.8%)	0	0	1	1 (0.4%)
Implant Procedure	2	2 (1.6%)	1	1 (0.8%)	3	3 (1.2%)
Explant Procedure	1	1 (0.8%)	0	0	1	1 (0.4%)
Charger	0	0	0	0	0	0
Stimulation Therapy	0	0	0	0	0	0
Indeterminate [3]	0	0	0	0	0	0
Deaths	0	0	0	0	0	0
UADE	0	0	0	0	0	0

Abbreviations: AE, adverse event; SAE, serious adverse event.

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

[1] Event counted as unrelated if classified as "unlikely related" or "not related to the implant device, implant procedure, explant procedure, Charger, *and* stimulation therapy

[2] Event counted as related if classified as "definitely related" or "probably related" to the implant device, implant procedure, explant procedure, Charger, *and/or* stimulation therapy

[3] Indeterminate means there is insufficient information about the event to arrive at a conclusion on causal relationship. Event counted as indeterminate if *not* counted as related and classified as "indeterminate" to the implant device, implant procedure, explant procedure, Charger, *and/or* stimulation therapy

[4] An event can be classified as related in more than 1 category (e.g., implant device and procedure)

Table S12: Non-Serious, Unrelated AEs from Implant to 3 Months with Frequency >3%

MedDRA Preferred Term	Arm 1: Stimulation (N=122) n (%)	Arm 2: Sham (N=120) n (%)	All (N=243) n (%)
Subject with AE	67 (54.9%)	76 (63.3%)	143 (58.8%)
COVID-19	8 (6.6%)	6 (5%)	14 (5.8%)
Arthralgia	4 (3.3%)	1 (0.8%)	5 (2.1%)
Sinusitis	3 (2.5%)	4 (3.3%)	7 (2.9%)
Nausea	2 (1.6%)	4 (3.3%)	6 (2.5%)
Bronchitis	1 (0.8%)	4 (3.3%)	5 (2.1%)
Neck pain	1 (0.8%)	4 (3.3%)	5 (2.1%)
Dizziness	0	4 (3.3%)	4 (1.6%)
Headache	0	4 (3.3%)	4 (1.6%)
Given in the table are number of subjects, with percentage, experiencing events for each AE category. At each level of summation, subjects are counted only once.			

Table S13: Non-Serious, Implant Procedure/Device Related AEs from Implant to 3 Months

MedDRA Preferred Term	Arm 1: Stimulation (N=122) n (%)	Arm 2 Sham (N=120) n (%)	All (N=243) n (%)
Subject with AE	17 (13.9%)	22 (18.3%)	39 (16%)
Vocal cord paresis	5 (4.1%)	6 (5%)	11 (4.5%)
Dysphonia	4 (3.3%)	3 (2.5%)	7 (2.9%)
Cough	1 (0.8%)	0	1 (0.4%)
Diarrhea	1 (0.8%)	0	1 (0.4%)
Dysphagia	1 (0.8%)	2 (1.7%)	3 (1.2%)
Dyspnea	1 (0.8%)	0	1 (0.4%)
GI complication associated with device	1 (0.8%)	0	1 (0.4%)
Implant site hypoesthesia	1 (0.8%)	1 (0.8%)	2 (0.8%)
Implant site inflammation	1 (0.8%)	1 (0.8%)	2 (0.8%)
Implant site swelling	1 (0.8%)	2 (1.7%)	3 (1.2%)
Medical device site swelling	1 (0.8%)	0	1 (0.4%)
Migraine	1 (0.8%)	0	1 (0.4%)
Postoperative wound infection	1 (0.8%)	0	1 (0.4%)
Rash	1 (0.8%)	1 (0.8%)	2 (0.8%)
Scar pain	1 (0.8%)	0	1 (0.4%)
Stitch abscess	1 (0.8%)	0	1 (0.4%)

MedDRA Preferred Term	Arm 1: Stimulation (N=122) n (%)	Arm 2 Sham (N=120) n (%)	All (N=243) n (%)
Swelling	1 (0.8%)	0	1 (0.4%)
Swelling of eyelid	1 (0.8%)	1 (0.8%)	2 (0.8%)
Application site rash	0	2 (1.7%)	2 (0.8%)
Eyelid ptosis	0	1 (0.8%)	1 (0.4%)
Headache	0	1 (0.8%)	1 (0.4%)
Implant site erythema	0	1 (0.8%)	1 (0.4%)
Implant site pain	0	2 (1.7%)	2 (0.8%)
Oropharyngeal pain	0	1 (0.8%)	1 (0.4%)
Procedural pain	0	1 (0.8%)	1 (0.4%)
Suture related complication	0	1 (0.8%)	1 (0.4%)
Thrombophlebitis superficial	0	1 (0.8%)	1 (0.4%)

Abbreviation: GI=Gastrointestinal
Given in the table are number of subjects, with percentage, experiencing events for each AE category. At each level of summation, subjects are counted only once.

Table S14: Non-Serious, Stimulation-Related AEs from Randomization to 3 Months

MedDRA Preferred Term	Arm 1: Stimulation (N=122) n (%)	Arm 2: Sham [1] (N=120) n (%)	All (N=243) n (%)
Subject with AE	10 (8.2%)	0	10 (4.1%)
Medical device pain	4 (3.3%)	0	4 (1.6%)
Choking sensation	1 (0.8%)	0	1 (0.4%)
Cough	1 (0.8%)	0	1 (0.4%)
Dysgeusia	1 (0.8%)	0	1 (0.4%)
Oropharyngeal pain	1 (0.8%)	0	1 (0.4%)
Procedural nausea	1 (0.8%)	0	1 (0.4%)
Retching	1 (0.8%)	0	1 (0.4%)
Toothache	1 (0.8%)	0	1 (0.4%)

Given in the table are number of subjects, with percentage, experiencing events for each AE category. At each level of summation, subjects are counted only once.
[1] There were 6 AEs classified by the Co-PI Rheumatologist as related to stimulation that were reclassified to "not related" once the database was locked, the study was unblinded, and it was determined the subjects experiencing these AEs has been assigned to the control group. This reassignment was done in accordance with the study protocol: CLP-001, Section 15.2.2. The following evets were reclassified: worsening chronic back pain, intermittent lightheadedness, hoarseness, tingling left side of neck, hoarseness/loss of voice, slight headaches, consistent. Change was only made to the relationship to stimulation. Relationships to implant device, implant procedure, explant procedure, or Charger were not changed.

Table S15: Serious, Unrelated AEs from Implant to 3 Months

MedDRA Preferred Term	Arm 1: Stimulation (N=122) n (%)	Arm 2: Sham (N=120) n (%)	All (N=243) n (%)
Subject with SAE	2 (1.6%)	4 (3.3%)	6 (2.5%)
Cervical spinal stenosis	1 (0.8%)	0	1 (0.4%)
Gastrointestinal hemorrhage	1 (0.8%)	0	1 (0.4%)
Osteomyelitis acute	0	1 (0.8%)	1 (0.4%)
Sternal fracture	0	1 (0.8%)	1 (0.4%)
Swollen tongue	0	1 (0.8%)	1 (0.4%)
Thoracic vertebral fracture	0	1 (0.8%)	1 (0.4%)
Trigeminal neuralgia	0	1 (0.8%)	1 (0.4%)

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

Table S16: Serious, Procedure/Device-Related AEs from Implant to 3 Months

MedDRA Preferred Term	Arm 1: Stimulation (N=122) n (%)	Arm 2: Sham (N=120) n (%)	All (N=243) n (%)
Subject with AE	3 (2.5%)	1 (0.8%)	4 (1.6%)
Incision site swelling [1]	1 (0.8%)	0	1 (0.4%)
Vocal cord paresis [1]	1 (0.8%)	0	1 (0.4%)
Dysphonia [1]	0	1 (0.8%)	1 (0.4%)
Pharyngeal perforation [2]	1 (0.8%)	0	1 (0.4%)

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

[1] Procedure-related, onset prior to randomization: incision site swelling hospitalized for evaluation that ruled out infection (resolved); vocal cord paresis with dysphagia that led to hospitalization (resolved); dysphonia deemed by investigator significant enough to impair daily activities (resolved, mild sequelae).

[2] Occurred during explant procedure, repaired intraoperatively, no hospitalization required (resolved).

Table S17: Implant Duration for Long-Term Follow-Up*

Type of Exposure	Arm 1	Arm 2
N	122	120
Mean (days)	753	751
Median (days)	672	663
Min, Max (days)	141, 1432	210, 1503

*Data cut-off for safety reported in the Supplemental Appendix is March 10, 2025, unless otherwise noted.

Table S18: Adverse Events in Long-Term Follow-Up

AE category	Arm 1 (N=121)		Arm 2 (N=120)		All (N=241)	
	Events	Subjects n (%)	Events	Subjects n (%)	Events	Subjects N (%)
Any non-serious AE	421	93 (76.9%)	402	100 (83.3%)	823	193 (80.1%)
Unrelated [1]	406	92 (76%)	385	96 (80%)	791	188 (78%)
Related [2], [4]	7 [5]	7 (5.8%)	6	6 (5.0%)	13	13 (5.4%)
Implant Device	1	1 (0.8%)	1	1 (0.8%)	2	2 (0.8%)
Implant Procedure	0	0	1	1 (0.8%)	1	1 (0.4%)
Explant Procedure	0	0	0	0	0	0
Charger	1	1 (0.8%)	0	0	1	1 (0.4%)
Stimulation Therapy	6	6 (5.0%)	5	5 (4.2%)	11	11 (4.6%)
Indeterminate [3]	9	8 (6.6%)	12	9 (7.5%)	21	17 (7.1%)
Any SAE	31	18 (14.9%)	50	27 (22.5%)	81	45 (18.7%)
Unelated [1]	31	18 (14.9%)	50	27 (22.5%)	81	45 (18.7%)
Related [2], [4]	0	0	0	0	0	0
Implant Device	0	0	0	0	0	0
Implant Procedure	0	0	0	0	0	0
Explant Procedure	0	0	0	0	0	0
Charger	0	0	0	0	0	0
Stimulation Therapy	0	0	0	0	0	0
Indeterminate [3]	0	0	1	1 (0.8%)	1	1 (0.4%)
Deaths	0	0	0	0	0	0
UADE	0	0	0	0	0	0

Abbreviations: AE, adverse event; SAE, serious adverse event.

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

[1] Event counted as unrelated if classified as "unlikely related" or "not related to the implant device, implant procedure, explant procedure, Charger, and stimulation therapy

[2] Event counted as related if classified as "definitely related" or "probably related" to the implant device, implant procedure, explant procedure, Charger, and/or stimulation therapy

[3] Indeterminate means there is insufficient information about the event to arrive at a conclusion on causal relationship. Event counted as indeterminate if not counted as related and classified as "indeterminate" to the implant device, implant procedure, explant procedure, Charger, and/or stimulation therapy

[4] An event can be classified as related in more than 1 category (e.g., implant device and procedure)

Table S19: Non-Serious, Unrelated AEs during Long-Term Follow-up with Frequency >3%

MedDRA Preferred Term	Arm 1 (N=121) n (%)	Arm 2 (N=120) n (%)	All (N=241) n (%)
Subject with AE	92 (76%)	96 (80%)	188 (78%)
COVID-19	18 (14.9%)	23 (19.2%)	41 (17%)
Arthralgia	10 (8.3%)	8 (6.7%)	18 (7.5%)
Nasopharyngitis	10 (8.3%)	5 (4.2%)	15 (6.2%)
Upper respiratory tract infection	10 (8.3%)	2 (1.7%)	12 (5%)
Sinusitis	9 (7.4%)	8 (6.7%)	17 (7.1%)
Urinary tract infection	8 (6.6%)	10 (8.3%)	18 (7.5%)
Osteoarthritis	7 (5.8%)	8 (6.7%)	15 (6.2%)
Anaemia	6 (5%)	4 (3.3%)	10 (4.1%)
Carpal tunnel syndrome	5 (4.1%)	2 (1.7%)	7 (2.9%)
Bursitis	4 (3.3%)	2 (1.7%)	6 (2.5%)
Nerve compression	4 (3.3%)	0 (0%)	4 (1.7%)
Hypertension	3 (2.5%)	4 (3.3%)	7 (2.9%)
Influenza	3 (2.5%)	6 (5%)	9 (3.7%)
Joint injury	3 (2.5%)	4 (3.3%)	7 (2.9%)
Cough	2 (1.7%)	5 (4.2%)	7 (2.9%)
Rotator cuff syndrome	2 (1.7%)	4 (3.3%)	6 (2.5%)
Depression	1 (0.8%)	6 (5%)	7 (2.9%)
Pain	1 (0.8%)	4 (3.3%)	5 (2.1%)
Given in the table are number of subjects, with percentage, experiencing events for each AE category. At each level of summation, subjects are counted only once.			

Table S20: Non-serious, Stimulation-Related AEs during Long-Term Follow-Up

MedDRA Preferred Term	Arm 1 (N=121) n (%)	Arm 2 (N=120) n (%)	All (N=241) n (%)
Subject with AE	6 (5.0%)	5 (4.2%)	11 (4.6%)
Poor quality sleep	2 (1.7%)	0 (0%)	2 (0.8%)
Implant site paraesthesia	1 (0.8%)	0 (0%)	1 (0.4%)
Medical device discomfort	1 (0.8%)	0 (0%)	1 (0.4%)
Medical device site discomfort	1 (0.8%)	0 (0%)	1 (0.4%)
(exacerbation of) Trigeminal neuralgia [1]	1 (0.8%)	0 (0%)	1 (0.4%)
Dysphonia	0 (0%)	1 (0.8%)	1 (0.4%)
Implant site pain	0 (0%)	1 (0.8%)	1 (0.4%)

MedDRA Preferred Term	Arm 1 (N=121) n (%)	Arm 2 (N=120) n (%)	All (N=241) n (%)
Muscle spasms	0 (0%)	1 (0.8%)	1 (0.4%)
Presyncope	0 (0%)	1 (0.8%)	1 (0.4%)
Temporomandibular joint syndrome	0 (0%)	1 (0.8%)	1 (0.4%)

[1] Exacerbation of neuralgic symptoms of trigeminal neuralgia.
Given in the table are number of subjects, with percentage, experiencing events for each AE category. At each level of summation, subjects are counted only once.

Table S21: Cumulative Serious, Unrelated AEs during Long-Term Follow-up

MedDRA SOC	Arm 1 (N=121) n (%)	Arm 2 (N=120) n (%)	All (N=241) n (%)
Subject with SAE	18 (14.9%)	27 (22.5%)	45 (18.7%)
Cardiac disorders	4 (3.3%)	2 (1.7%)	6 (2.5%)
Gastrointestinal disorders	4 (3.3%)	1 (0.8%)	5 (2.1%)
Infections and infestations	4 (3.3%)	11 (9.2%)	15 (6.2%)
Renal and urinary disorders	3 (2.5%)	3 (2.5%)	6 (2.5%)
Injury, poisoning and procedural complications	2 (1.7%)	5 (4.2%)	7 (2.9%)
Investigations	2 (1.7%)	0 (0%)	2 (0.8%)
Musculoskeletal and connective tissue disorders	2 (1.7%)	3 (2.5%)	5 (2.1%)
Hepatobiliary disorders	1 (0.8%)	1 (0.8%)	2 (0.8%)
Neoplasm benign/malignant, unspecified (incl cysts/polyps)	1 (0.8%)	2 (1.7%)	3 (1.2%)
Nervous system disorders	1 (0.8%)	3 (2.5%)	4 (1.7%)
Respiratory, thoracic and mediastinal disorders	1 (0.8%)	1 (0.8%)	2 (0.8%)
Vascular disorders	1 (0.8%)	0 (0%)	1 (0.4%)
Blood and lymphatic system disorders	0 (0%)	3 (2.5%)	3 (1.2%)
Eye disorders	0 (0%)	1 (0.8%)	1 (0.4%)
General disorders and administration site conditions	0 (0%)	2 (1.7%)	2 (0.8%)
Metabolism and nutrition disorders	0 (0%)	1 (0.8%)	1 (0.4%)
Psychiatric disorders	0 (0%)	2 (1.7%)	2 (0.8%)
Reproductive system and breast disorders	0 (0%)	1 (0.8%)	1 (0.4%)

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

Serious, Related Adverse Events in Long-Term Follow-Up

NOTE: There were no serious, related adverse events during long-term follow-up.

Changes in Hematology and Vital Signs

Table S22: Mean Changes in Hematology Values

Analyte	Arm 1 (N=122)		Arm 2 (N=120)	
	n	Mean (SD)	n	Mean (SD)
Change from Screening				
Absolute Neutrophil Count (x10/L)				
3 months	116	0.18 (1.81)	112	0.23 (2.34)
6 months	117	0.32 (1.96)	114	0.51 (2.05)
9 months	109	0.03 (2.03)	106	0.08 (2.07)
12 months	111	0.15 (2.05)	105	0.13 (1.97)
Hematocrit (Ratio)				
3 months	116	-0.01 (0.03)	112	-0.01 (0.03)
6 months	117	0 (0.04)	114	-0.01 (0.03)
9 months	109	0 (0.03)	106	-0.01 (0.03)
12 months	112	0 (0.03)	105	0 (0.03)
Hemoglobin (g/dL)				
3 months	116	-0.18 (0.76)	112	-0.23 (0.89)
6 months	117	-0.08 (1.01)	115	-0.25 (0.96)
9 months	109	-0.06 (1.00)	106	-0.28 (0.89)
12 months	112	0.01 (0.99)	105	-0.16 (1.04)
Platelets (x10/L)				
3 months	109	10.33 (57.06)	106	4.87 (54.56)
6 months	107	1.1 (57.49)	106	3.19 (64.59)
9 months	104	3.45 (65.4)	102	-7.66 (62.49)
12 months	107	2.03 (49.33)	103	-6.54 (61.46)
Leukocytes (x10/L)				
3 months	116	-0.02 (1.8)	112	0.18 (2.21)
6 months	117	0.19 (2)	114	0.36 (2.04)
9 months	109	-0.07 (2.18)	106	0.06 (2.10)
12 months	112	0.07 (2.09)	105	0.1 (2.07)
Change from Day 0				
Absolute Neutrophil Count (x10/L)				

Analyte	Arm 1 (N=122)		Arm 2 (N=120)	
	n	Mean (SD)	n	Mean (SD)
3 months	116	0.25 (1.59)	107	-0.11 (2.07)
6 months	117	0.35 (1.86)	109	0.1 (2.24)
9 months	109	0.07 (1.60)	101	-0.39 (2.09)
12 months	110	0.27 (1.86)	100	-0.22 (2.16)
Hematocrit (Ratio)				
3 months	116	0 (0.03)	109	0 (0.03)
6 months	117	0.01 (0.03)	111	0 (0.03)
9 months	109	0.01 (0.03)	103	0 (0.03)
12 months	111	0.01 (0.03)	102	0 (0.03)
Hemoglobin (g/dL)				
3 months	117	-0.06 (0.77)	111	-0.09 (0.71)
6 months	118	0.06 (0.92)	114	-0.09 (0.78)
9 months	110	0.09 (1.02)	105	-0.12 (0.81)
12 months	112	0.15 (1.05)	104	-0.05 (0.97)
Platelets (x10/L)				
3 months	108	2.83 (50.07)	106	-5.3 (52.12)
6 months	106	-6.78 (55.87)	106	-8.16 (52.07)
9 months	102	-4.71 (62.88)	100	-18.33 (66.78)
12 months	106	-4.11 (55.18)	101	-18.8 (64.82)
Leukocytes (x10/L)				
3 months	116	0.2 (1.53)	109	-0.1 (2.12)
6 months	117	0.34 (1.87)	111	0 (2.14)
9 months	109	0.1 (1.75)	103	-0.3 (2.07)
12 months	111	0.32 (1.93)	102	-0.19 (2.19)
Change from 3 Months				
Absolute Neutrophil Count (x10/L)				
6 months	117	0.32 (1.96)	114	0.51 (2.05)
9 months	109	0.03 (2.03)	106	0.08 (2.07)
12 months	111	0.5 (2.05)	105	0.13 (1.97)
Hematocrit (Ratio)				
6 months	117	0 (0.04)	114	-0.01 (0.03)
9 months	109	0 (0.03)	106	-0.01 (0.03)
12 months	112	0 (0.03)	105	0 (0.03)
Hemoglobin (g/dL)				
6 months	117	-0.08 (1.01)	115	-0.25 (0.96)

Analyte	Arm 1 (N=122)		Arm 2 (N=120)	
	n	Mean (SD)	n	Mean (SD)
9 months	109	-0.06 (1.00)	106	-0.28 (0.89)
12 months	112	0.01 (0.99)	105	-0.16 (1.04)
Platelets (x10/L)				
6 months	107	1.1 (57.49)	106	3.19 (64.59)
9 months	104	3.45 (65.4)	102	-7.66 (62.49)
12 months	107	2.03 (49.33)	103	-6.54 (61.46)
Leukocytes (x10/L)				
6 months	117	0.19 (2.00)	114	0.36 (2.04)
9 months	109	-0.07 (2.18)	106	0.06 (2.10)
12 months	112	0.07 (2.09)	105	0.1 (2.07)

Table S23: Mean Changes in Vital Sign Values

Vital Sign	Arm 1 (N=122)		Arm 2 (N=120)	
	n	Mean (SD)	n	Mean (SD)
Change from Screening				
Diastolic Blood Pressure (mmHg)				
3 months	120	-0.52 (9.38)	117	0.44 (9.29)
6 months	118	-1.33 (9.16)	116	-0.78 (9.01)
9 months	118	-1.03 (9.96)	114	0.95 (10.08)
12 months	118	-1.36 (9.99)	113	0.32 (9.74)
Systolic Blood Pressure (mmHg)				
3 months	120	-1.8 (14.15)	117	-0.79 (14.74)
6 months	118	-1.97 (13.16)	116	-1.7 (14.33)
9 months	118	-4.26 (14.08)	114	-1.54 (14.61)
12 months	118	-4.64 (12.9)	113	-0.42 (15.69)
Pulse Rate (bpm)				
3 months	120	1.14 (10.63)	117	2.85 (12.34)
6 months	118	1.31 (9.76)	116	1.67 (11.22)
9 months	118	1.53 (12.09)	114	1.98 (11.46)
12 months	118	2.14 (11.98)	113	2.04 (10.71)
Respiratory Rate (/min)				
3 months	119	-0.15 (2.21)	117	0.58 (2.37)
6 months	118	-0.08 (2.09)	116	0.14 (2.16)

Vital Sign	Arm 1 (N=122)		Arm 2 (N=120)	
	n	Mean (SD)	n	Mean (SD)
9 months	117	-0.38 (2.26)	114	0.47 (2.52)
12 months	117	-0.1 (2.49)	113	0.01 (2.73)
Weight (lbs.)				
3 months	119	0.51 (8.43)	119	0.25 (6.98)
6 months	117	0.35 (12.29)	115	0.47 (9.05)
9 months	119	-2.42 (18.74)	115	-0.26 (10.5)
12 months	119	-1.07 (13.88)	114	-0.03 (12.1)
Change from Day 0				
Diastolic Blood Pressure (mmHg)				
3 months	118	-0.55 (9.56)	113	0.68 (8.78)
6 months	116	-1.42 (9.42)	111	-0.53 (9.09)
9 months	116	-1.37(9.17)	109	1.21 (10.71)
12 months	116	-1.53 (8.84)	108	0.61 (9.84)
Systolic Blood Pressure (mmHg)				
3 months	118	-0.41 (13.47)	113	0.81 (14.53)
6 months	116	-0.59 (13.78)	111	-0.04 (13.59)
9 months	116	-2.95 (13.91)	109	0.39 (13.93)
12 months	116	-3.1 (13.01)	108	1.4 (14.9)
Pulse Rate (bpm)				
3 months	118	-2.16 (10.68)	113	-1.3 (10.05)
6 months	116	-2.06 (9.28)	111	-2.41 (10.86)
9 months	116	-1.67 (11.33)	109	-2.23 (11.2)
12 months	116	-1.07 (12.03)	108	-2.1 (10.42)
Respiratory Rate (/min)				
3 months	117	-0.03 (2.1)	112	0.35 (2.22)
6 months	116	-0.03 (1.89)	110	-0.06 (2.1)
9 months	115	-0.21 (2.13)	108	0.19 (2.45)
12 months	115	0.03 (2.21)	107	-0.21 (2.39)
Weight (lbs.)				
3 months	114	1.21 (6.85)	112	1.18 (11.6)
6 months	112	0.78 (10.69)	108	1.12 (13.07)
9 months	114	-2.08 (19.2)	107	0.51 (14.45)
12 months	114	-0.69 (12.99)	106	0.66 (15.82)
Change from 3 Months				
Diastolic Blood Pressure (mmHg)				
6 months	119	-0.78 (9.28)	116	-1.32 (9.11)

Vital Sign	Arm 1 (N=122)		Arm 2 (N=120)	
	n	Mean (SD)	n	Mean (SD)
9 months	119	-0.59 (9.69)	113	0.4 (9.53)
12 months	119	-0.89 (9.65)	112	-0.28 (9.62)
Systolic Blood Pressure (mmHg)				
6 months	119	0.38 (13.03)	116	-0.91 (13.37)
9 months	119	-2.28 (14.1)	113	-0.81 (14.02)
12 months	119	-2.57 (13.86)	112	-0.04 (15.57)
Pulse Rate (bpm)				
6 months	119	-0.18 (9.83)	116	-1.41 (9.46)
9 months	119	0.08 (9.31)	113	-0.97 (10.25)
12 months	119	0.67 (10.81)	112	-1.49 (9.71)
Respiratory Rate (/min)				
6 months	118	0.03 (2.00)	116	-0.46 (2.16)
9 months	117	-0.25 (2.54)	113	-0.14 (2.49)
12 months	117	0.03 (2.05)	112	-0.63 (2.38)
Weight (lbs.)				
6 months	116	-0.1 (7.51)	115	0 (5.7)
9 months	117	-2.89 (17.36)	114	-0.72 (8.76)
12 months	117	-1.46 (10.42)	113	-0.59 (11.01)

Table S24: Study Period

First Randomization Day 0, about 14-21 days after Implant Procedure	**Last Week 12 visit** primary/secondary endpoints	**Last Week 24 visit** open-label outcomes
22 February 2021	16 May 2024	08 August 2024