Neuroimmune Modulation for the Treatment of Rheumatoid Arthritis: Long-term Results at 24 Months from a Randomized, Sham-Controlled, Double-Blind Trial

John R.P. Tesser[1], Angela R. Crowley[2], Emily Jane Box[3], Joshua P. June[4], Pendleton Brewster Wickersham[5], Guillermo J. Valenzuela[6], Norman B. Gaylis[7], Gordon K.W. Lam[8], Leroy A. Pacheco[9], David J. Ridley[10], Gineth Paola Pinto-Patarroyo[11], Stuart N. Novack[12], Melvin A. Churchill[13], Minna Kohler[14], Eric C. Lee[15], Jose A. Pando[16], Glenn R. Parris[17], Jeff R. Peterson[18], Tina Shah[19], Atul K. Singhal[20], Victoria Vuong[21], Jeffrey R. Curtis[22], David Chernoff[23]

[1]Arizona Arthritis & Rheumatology Research, Avondale, AZ, [2]Willow Rheumatology and Wellness, Willowbrook, IL, [3]DJL Clinical Research, Charlotte, NC, [4]Great Lakes Center of Rheumatology, Lansing, MI, [5]Flourish Research, San Antonio, TX, [6]IRIS Research and Development, Plantation, FL, [7]Arthritis & Rheumatic Disease Specialties, Aventura, FL, [8]Arthritis & Osteoporosis Consultants of the Carolinas, Charlotte, NC, [9]Albuquerque Center for Rheumatology, Albuquerque, NM, [10]St. Paul Rheumatology, Eagan, MN, [11]Annapolis Rheumatology, Fairfax, VA, [12]Stamford Therapeutics Consortium, Stamford, CT, [13]Physician Research Collaboration, Lincoln, NE, [14]Massachusetts General Hospital, Boston, MA, [15]Inland Rheumatology Clinical Trials, Upland, CA, [16]Delaware Arthritis, Lewes, DE, [17]Parris and Associates Rheumatology, Atlanta, GA, [18]Western Washington Medical Group, Rheumatology Bothell, Bothell, WA, [19]Kansas City Physician Partners, Kansas City, MO, [20]Southwest Rheumatology Research, Mesquite, TX, [21]Long Island Regional Arthritis & Osteoporosis Care, Babylon, NY, [22]University of Alabama at Birmingham, Birmingham, AL, [23]SetPoint Medical, Corp., Valencia, CA

SUMMARY

Vagus-mediated neuroimmune modulation represents a novel treatment modality for patients with RA. The RESET-RA study evaluated the safety and efficacy of an implantable neuroimmune modulation device in patients with inadequate response or intolerance to at least one (1) b/tsDMARD.

The study met its primary endpoint of ACR20 at 3 months in biologic-experienced RA patients (average 12 years of disease and 2.5 prior biologics). In long-term RA management, vagus-mediated neuroimmune modulation provided durable, consistent clinical benefit through 24 months, with most patients avoiding b/tsDMARDs. Of those managed with neuroimmune modulation therapy without add-on therapy, ~50% were in LDA or remission at 24 months.

Kinetics of response differ from typical RA treatments; MOA downregulates multiple cytokines by 30-70%. At 3 months, structural joint protection and clinically and statistically significant differences in disease activity measurements were observed. Meaningful disease activity improvements were observed at 6-9 months and continue to improve through 24 months. This is consistent with kinetics of the differentiated MOA.

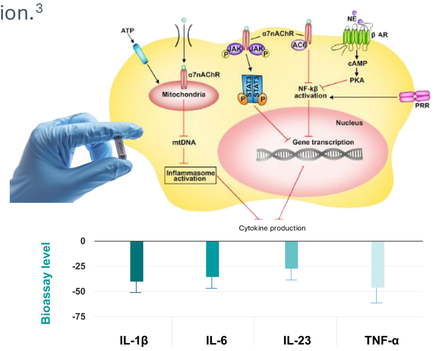
No new safety concerns were identified. The high therapy persistence rate reflects the tolerability of this implantable device, offering a differentiated therapeutic approach for treatment of RA.

INTRODUCTION

Vagus-mediated neuroimmune reflex downregulates inflammatory cytokines, providing a novel treatment approach for managing autoimmune conditions like RA.[1,2] The vagus nerve also releases specialized pro-resolving mediators to aid resolution of inflammation by decreasing proinflammatory cytokines while increasing clearance of cellular debris and improving joint protection.[3]

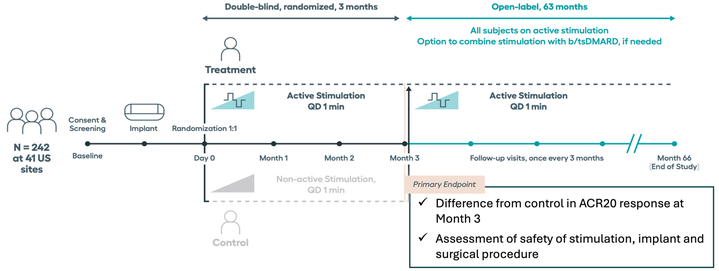
Activating this reflex with a 60-second stimulation inhibits intracellular pathways to suppress multiple inflammatory cytokines by 30-70%, with sustained reduction for 24-48 hours post stimulation.[2,4]

The implantable neuroimmune modulation device is designed to activate these neuroimmune pathways. It is placed on the left cervical vagus nerve in an outpatient procedure and programmed to deliver automatic stimulation for one minute, daily.



STUDY DESIGN AND BASELINE DEMOGRAPHICS

RESET-RA study was designed to assess the safety and efficacy of an implanted neuroimmune modulation device to treat adults with active, moderate to severe RA who have had an inadequate response, loss of response, or intolerance to 1 or more b/tsDMARDs. (NCT04539964). Baseline demographics and characteristics were well-balanced and representative of a typical US RA population. On average, patients failed 2.5 prior b/tsDMARDs.



Patients were randomized 1:1 to receive active or sham stimulation for 60 seconds each day. A formal blinding assessment, using a validated statistical method (Bang's Blinding Index), was conducted, confirming that the study was successfully blinded.

	Control (N=120)	Treatment (N=122)
Age (years)		
Mean (SD)	55.5 (10.49)	55.8 (10.28)
Gender		
% Female	91.7%	80.3%
RA duration (years)		
Mean (SD)	11.8 (10.45)	13.0 (10.59)
CDAI score (0-76)		
Mean (SD)	38.2 (12.75)	36.1 (12.60)
DAS28-CRP score (0-9.4)		
Mean (SD)	5.4 (0.96)	5.3 (0.91)
csDMARD background therapy		
Methotrexate	45 (37.5%)	52 (42.6%)
Hydroxychloroquine	29 (24.2%)	26 (21.3%)
Leflunomide	17 (14.2%)	10 (8.2%)
Sulfasalazine	4 (3.3%)	4 (3.3%)
Combination	23 (19.2%)	29 (23.8%)
Number of prior b/tsDMARDs		
Mean (SD)	2.7 (1.87)	2.5 (1.98)
1	42 (35.0%)	52 (42.6%)
2	28 (23.3%)	25 (20.5%)
3+	50 (41.7%)	45 (36.9%)

RESULTS

At 3 months, a significantly greater percentage of patients in the treatment group were ACR20 responders (p=0.0209). At 24-month follow-up, 91.7% (222/242) continued with stimulation therapy; and 29.3% (71/242) had added a b/tsDMARD to stimulation therapy. ACR20 response rate for stimulation therapy without add-on therapy was 56.5%, 58.5%, and 62.7% at 12, 18, and 24 months, respectively **(Figure 1)**. At 24 months, ACR50 and ACR70 rates were 38.7% and 18.7%; LDA or remission was attained by 47.3% based on DAS28-CRP **(Figure 2)** and 48.3% by CDAI, while 77.7% met EULAR good or moderate response. Mean reduction in tender and swollen joint counts at 24 months were 57.6% and 66.3%, respectively **(Figure 3)**. After crossover through 24 months, no serious adverse events related to device or stimulation therapy were reported. The most common adverse event related to the device or stimulation therapy was mild to moderate pain occurring at the implant site in <5% of patients, that resolved on its own or with adjustment to stimulation or medication. A total of 14 patients (5.8%) underwent elective surgery to have the device removed primarily due to perceived lack of response (n=10). No deaths or unanticipated adverse device effects occurred **(Table 1)**.



Figure 1: Summary of ACR20 response through 24 months for patients with no add-on therapies after crossover. Modified non-responder imputation (NRI) data. Patients were imputed as non-responder if rescued prior to Month 3, regardless of treatment assignment. After Month 3, data presented for patients on non-augmented stimulation therapy. Data does not include subjects who received treatment with a biologic or targeted synthetic DMARD ("b/tsDMARD augmentation" subgroup) for the visit following initiation of the b/tsDMARD and every subsequent visit until the b/tsDMARD has ended and washed out (washout periods are drug dependent).

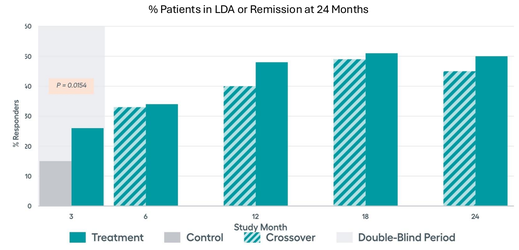


Figure 2: DAS28-CRP LDA or remission through 24 months for patients with no add-on therapies after crossover. Modified non-responder imputation (NRI) data. Patients were imputed as non-responder if rescued prior to Month 3, regardless of treatment assignment. After Month 3, data presented for patients on non-augmented stimulation therapy. Data does not include subjects who received treatment with a biologic or targeted synthetic DMARD ("b/tsDMARD augmentation" subgroup) for the visit following initiation of the b/tsDMARD and every subsequent visit until the b/tsDMARD has ended and washed out (washout periods are drug dependent).

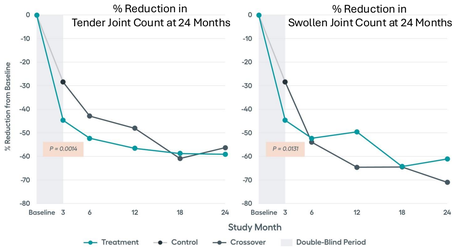


Figure 3: Mean percent reduction from baseline through 24 months for patients with no add-on therapies after crossover. Left: Mean percent reduction of tender joints from baseline. Right: Mean percent change of swollen joints from baseline. Modified non-responder imputation (NRI) data. Patients were imputed as non-responder if rescued prior to Month 3, regardless of treatment assignment. After Month 3, data presented for patients on non-augmented stimulation therapy. Data does not include subjects who received treatment with a biologic or targeted synthetic DMARD ("b/tsDMARD augmentation" subgroup) for the visit following initiation of the b/tsDMARD and every subsequent visit until the b/tsDMARD has ended and washed out (washout periods are drug dependent).

	3 - 24 Months		
	Crossover N=120	Treatment N=121	All N=241*
Number of pts (%) with Adverse Event	104 (86.7%)	97 (80.2%)	201 (83.4%)
Related Adverse Event[1,2]	6 (5.0%)	7 (5.8%)	13 (5.4%)
Related, Serious Adverse Event	0	0	0
Unrelated, Serious Adverse Event[3]	24 (20.0%)	16 (13.2%)	40 (16.6%)
AE Leading to Study Discontinuation[4]	3 (2.5%)	0	3 (1.2%)
Death	0	0	0

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

Given in the table are total number and percentage of participants experiencing each category of event. At each level of summation, participants are counted only once.

*Of the 242 randomized participants, one did not crossover to long-term follow-up.

[1]Related – 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.

[2]AEs included pain/discomfort (n=5), poor sleep quality (n=2) and one event (n=1) each of muscle spasm, dysphonia, temporomandibular joint syndrome, paresthesia, and presyncope. Managed by the adjustment of stimulation.

[3]Unrelated - event counted as unrelated if classified as "unlikely related" or "not related" to the implant device, implant procedure, explant procedure, Charger, or stimulation therapy.

[4]GI symptoms attributed to device/stimulation. Pain near implant attributed to the device. Head/neck cancer requiring radiation therapy.

Table 1: Summary of safety in long-term follow-up through 24 months.

References. [1] Lancet Rheumatol. 2020; 2:e527-538. [2] PNAS 2016; 113:8284-89. [3]Nat Rev Rheumatol. 2009 Apr;5(4):229-32. [4]Immunity. 2017; 46(1): 92–105.

Study sponsored by SetPoint Medical. **Disclosures:** JT: AbbVie, AstraZeneca, Boehringer-Ingelheim, BMS, Celgene, Cullinan, Eli Lilly, EnforceBio, Genentech, Gilead, GSK, IGM, ImpactBio, Janssen, Merck, Novartis, Pfizer, Roche, Sanofi, SecondWave, SetPoint Medical, UCB; AC: Artiva Biotherapeutics; JB: SetPoint Medical; JJ: Janssen, SetPoint Medical; PW: AbbVie, Amgen, AstraZeneca, Eli Lilly, Janssen, Novartis, SetPoint Medical, UCB; GV: AbbVie, Alexion, Amgen, Artiva, AstraZeneca, Boehringer-Ingelheim, BMS, Celgene, Centocor, Eli Lilly, Esaote, Exagen, Genentech, Gilead, GHLF, Horizon, Image Analysis Group, Janssen, Mallinckrodt, Merck, Novartis, Pfizer, Pharmacia, Radius, Regeneron, Sandoz, Sanofi, Takeda, Theramex, UCB, Vividion; NG: AB solutions, AbbVie, Acelyrin, Alumis, Amgen, Aqtual, Artiva, Biogen, BMS, Eli Lilly, Galapagos, Genentech, Gilead, GSK, Horizon, IGM, Inmedix, MoonLake, Novartis, Sanofi, SetPoint Medical, Takeda, UCB; GL: AbbVie, Amgen, Artiva, AstraZeneca, BMS, GSK, Janssen, Pfizer, Sanofi, SetPoint Medical, UCB; LP: AbbVie, Amgen, Eli Lilly, Horizon, Janssen, SetPoint Medical, UCB; DR: BMS, Eli Lilly, Janssen, UCB; GPP: None; SN: None; MC: None; MK: BMS, Pfizer, SetPoint Medical, Sobi, Sonoma, Springer; EL: None; JP: None; GP: None; JP: Amgen, Arthrosi, BMS, Eli Lilly, Johnson & Johnson, Novartis, Sobi, UCB; TS: AbbVie, Amgen, Johnson & Johnson, Merck, Novartis, Takeda, UCB; AS: Artiva; VV: AstraZeneca, Scipher, SetPoint Medical; JC: AbbVie, Amgen, AstraZeneca, Bendcare, Eli Lilly, FASTER, Genentech, GSK, Horizon, Janssen, Novartis, Pfizer, Roche, Sanofi, SetPoint Medical, UCB; DC: SetPoint Medical.