Trial of Vagus Nerve-Mediated Neuroimmune Modulation for Rheumatoid Arthritis

John Tesser, MD, FACP, FACR, MACR

September 20, 2025

VAGUS NERVE-MEDIATED NEUROIMMUNE MODULATION FOR RHEUMATOID ARTHRITIS

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Arizona Arthritis & Rheumatology Associates,

Phoenix, AZ

VSR 2025

John Tesser MD Disclosures

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Research Grants and Support

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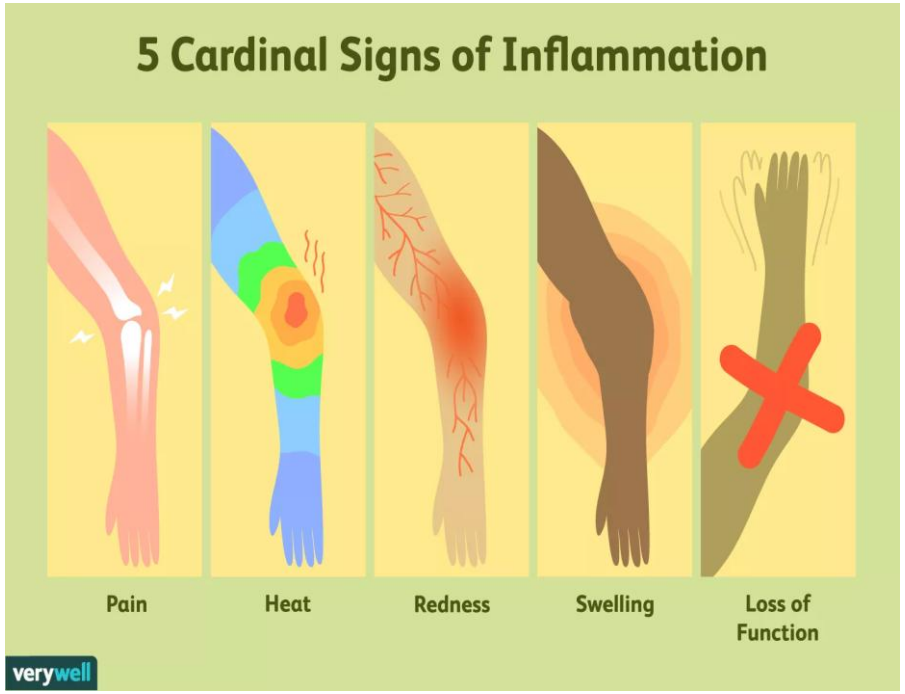
DISCLOSURES

- I am a clinical investigator and have served as the national principal investigator for the RESET-RA study and I serve as a consultant for SetPoint Medical
- RESET-RA study is sponsored by SetPoint Medical

The device discussed in the presentation is an implantable device that was approved by the FDA for commercial use: July 30, 2025

Inflammation

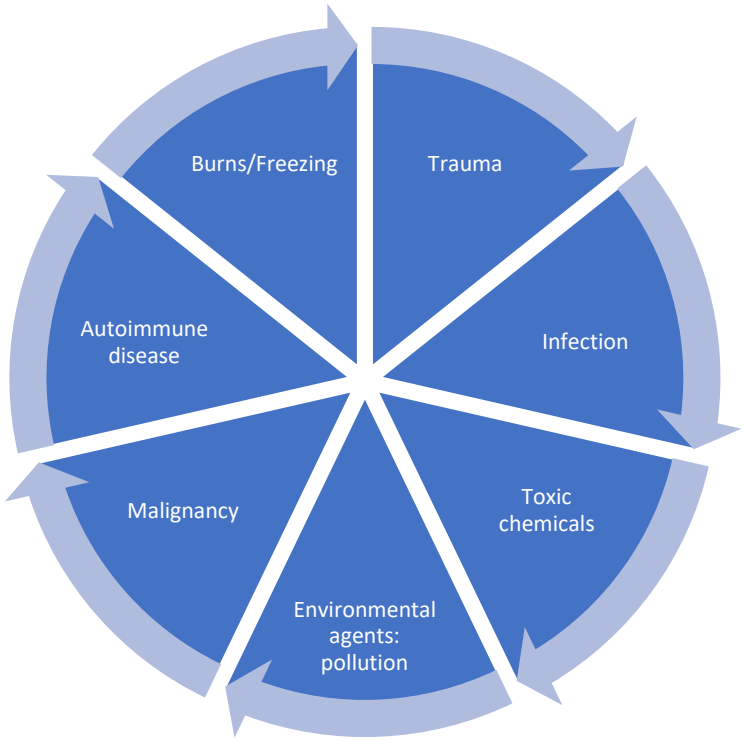


Merriam Webster
Medical Definition
in·flam·ma·tion ˌin-flə-ˈmā-shən
local response to cellular injury that is marked by capillary dilatation, leukocytic infiltration, redness, heat, pain, swelling, and often loss of function and that serves as a mechanism initiating the elimination of noxious agents and of damaged tissue

History
- 1st century BC: Roman polymath Celsus identified four signs of inflammation
- German physician Rudolf Virchow added loss of function

Inflammation

Responses to tissue injury: causes



Components of response

- Reactive oxygen species (ROS and RNOS)
- Formation of DNA adducts
- Cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha, and chemokines
- Acute-phase proteins, such as C-reactive protein or CRP
- Prostaglandins: Cyclooxygenase (COX)-related metabolites
- Inflammation-related growth factors and transcription factors, such as NF-kappaB
- Major immune cell types
- Blood vessels

Inflammation

- functions of inflammation
  - eliminate the initial cause of cell injury: infection, malignant cells
  - clear out damaged cells and tissues
  - initiate tissue repair
- Responses are keystone of pathology
  - Enough inflammation is good
  - Too much of a good thing is not good
- Primarily innate immune response
- Both cell mediated and humoral responses central
- Inflammaging

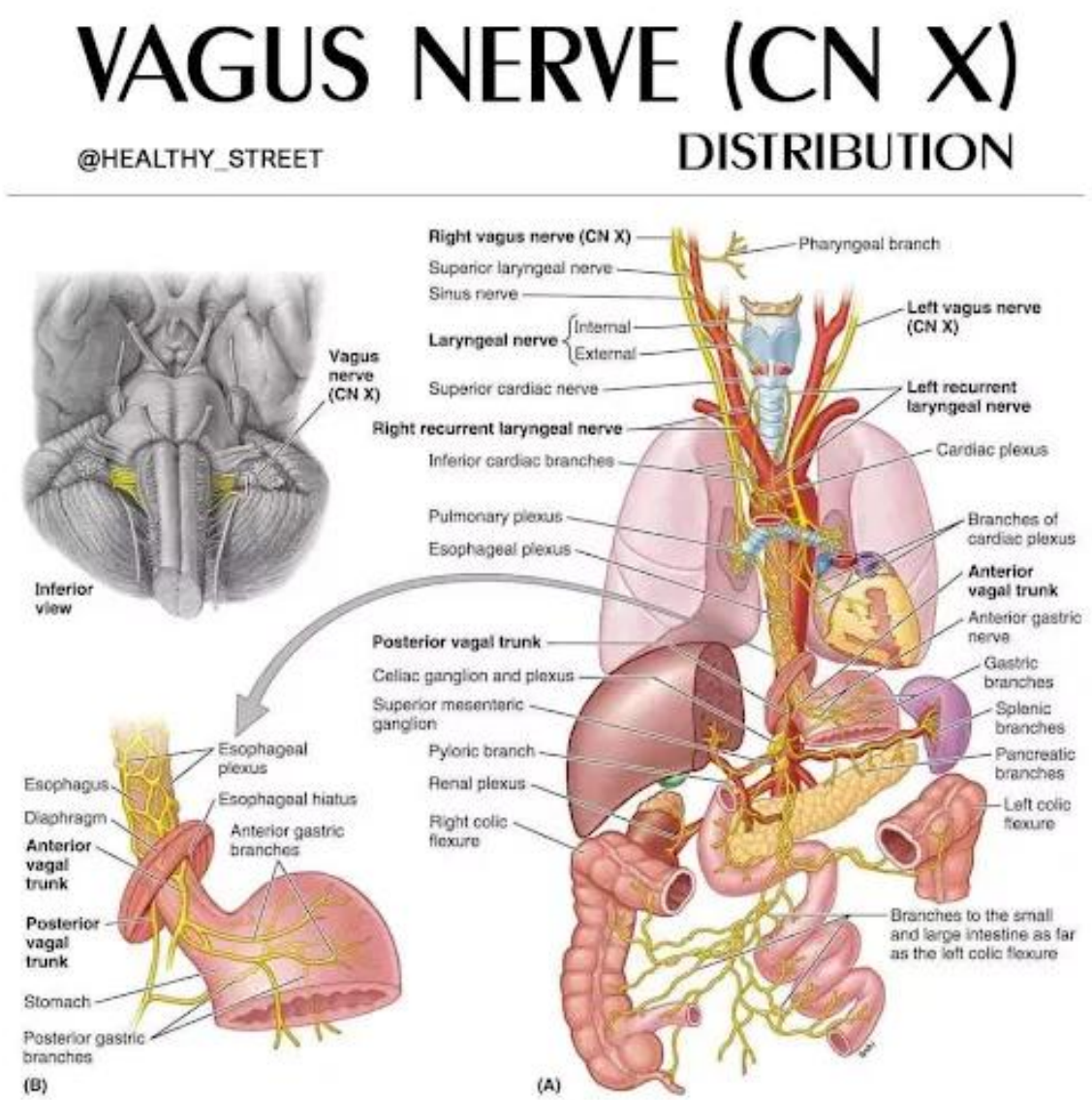
Stone WL, Basit H, Zubair M, et al. Pathology, Inflammation. [Updated 2024 Aug 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534820/

Li, X., Li, C., Zhang, W. *et al.* Inflammation and aging: signaling pathways and intervention therapies. *Sig Transduct Target Ther* **8**, 239 (2023). https://doi.org/10.1038/s41392-023-01502-8

THE VAGUS NERVE

Longest of the cranial nerves

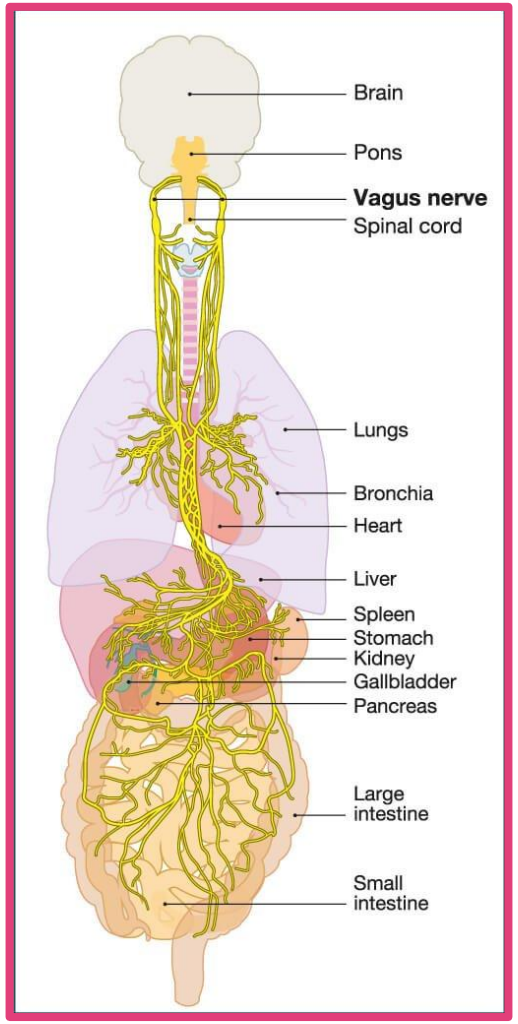
- Bilateral nerves that innervate multiple organs throughout the body (sensory and motor)
- Regulation of several important autonomic systems
  - Breathing
  - Heartrate
  - Digestion
- Regulation of the immune system



THE NEUROIMMUNE CONNECTION

The connection between the vagus nerve and the immune system

- Contralateral symptom improvement in RA patients with hemispheric stroke has been documented in case studies.[1]
- Decreased vagal tone has been identified as a precursor to developing RA.[2]
- Truncal vagotomy was associated with an increased risk of developing RA in Danish National Patient Registry.[3]

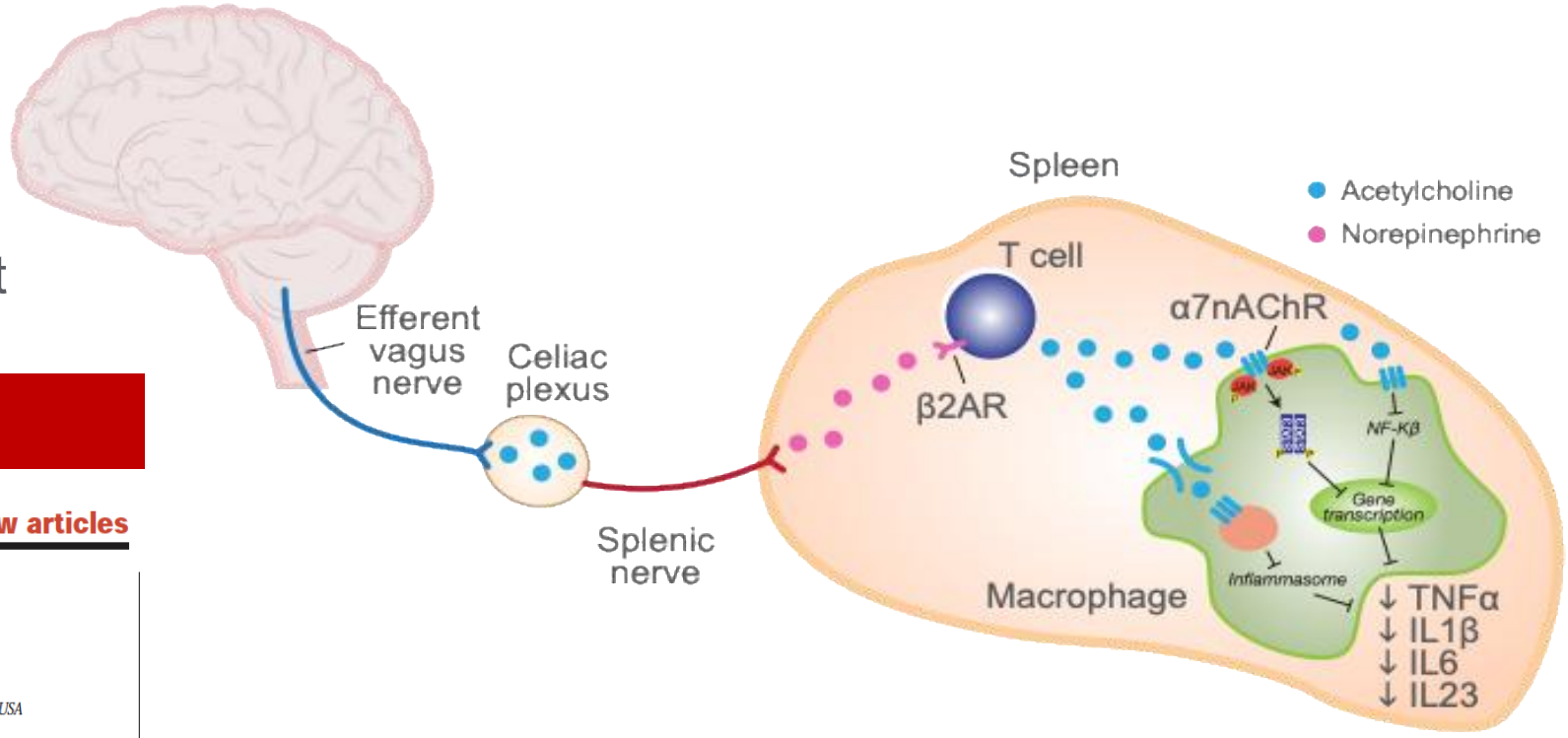


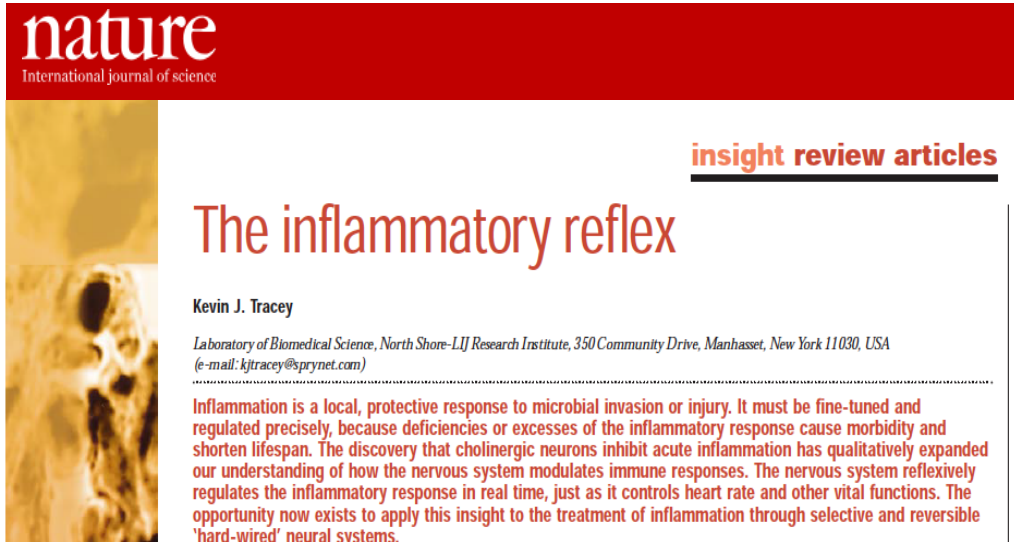
1. Ann. Rheum. Dis. 1962; 21, 370.
2. EBioMedicine. 2016;6:231-237.
3. Arthritis Rheumatol. 2023; 75 (suppl 9).

THE ESSENTIAL ROLE OF THE VAGUS NERVE

Vagus-nerve mediated neuroimmune modulation regulates innate immunity

- Vagus nerve senses infection, tissue injury, and relays information to central nervous system
- Inflammatory reflex regulates inflammation to maintain immunologic homeostasis, or “set point,” of the immune system





nature
International journal of science

insight review articles

The inflammatory reflex

Kevin J. Tracey

Laboratory of Biomedical Science, North Shore-LIJ Research Institute, 350 Community Drive, Manhasset, New York 11030, USA (e-mail: kjtracey@sprynet.com)

Inflammation is a local, protective response to microbial invasion or injury. It must be fine-tuned and regulated precisely, because deficiencies or excesses of the inflammatory response cause morbidity and shorten lifespan. The discovery that cholinergic neurons inhibit acute inflammation has qualitatively expanded our understanding of how the nervous system modulates immune responses. The nervous system reflexively regulates the inflammatory response in real time, just as it controls heart rate and other vital functions. The opportunity now exists to apply this insight to the treatment of inflammation through selective and reversible 'hard-wired' neural systems.

Nature. 2002; 402.

EVOLUTION OF NEUROIMMUME MODULATION

Cytokine discovery: from cachectin to TNF to neuroimmune modulation

Cytokine theory of disease hypothesized

Inflammatory reflex role in inflammation identified

Neuroimmune modulation techniques evaluated in RA

1987: Dr. Kevin Tracey publishes first ever use of TNFi antibodies to reduce systemic inflammation in baboon model of acute septic shock

1989: Dr. Feldmann and Dr. Maini publish the use of TNFi antibodies for treatment of RA

2000: Dr. Tracey hypothesizes that vagus nerve stimulation can reduce systemic inflammation

1998–99: Infliximab is first biologic approved for Crohn's Disease and RA

2016: First Proof of Concept study to evaluate neuroimmune modulation in RA disease activity with implantable device

2014: Dr. Charlie Serhan discovers classes of immunoresolving lipidomics linked to vagus nerve

2022: Proof of Concept splenic nerve stimulation study initiated

2021: FDA expands Black Box safety warning for entire class of JAKi drugs

2024: Large Ph. 3 RA study for neuroimmune modulation with implantable device meets primary endpoint

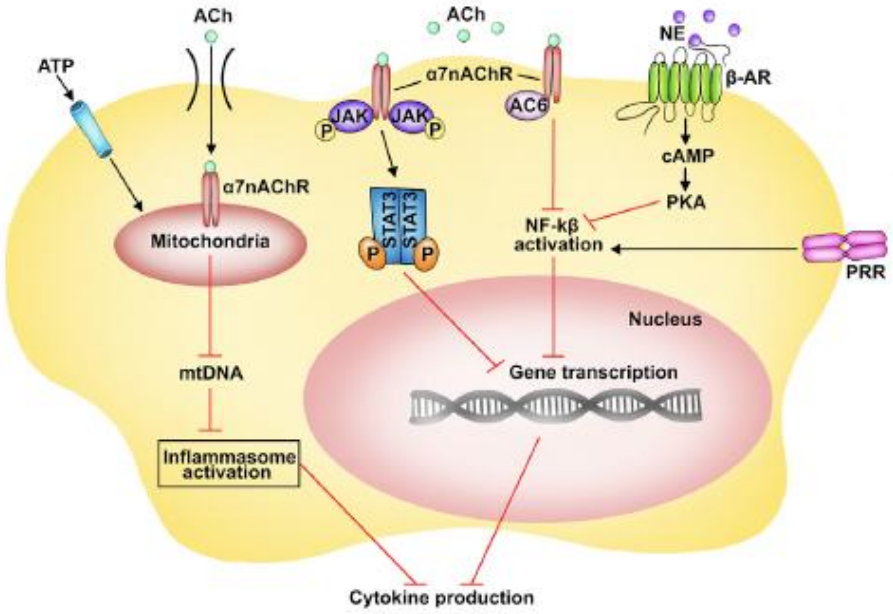
2023: Auricular VNS study shows no improvement in RA over control

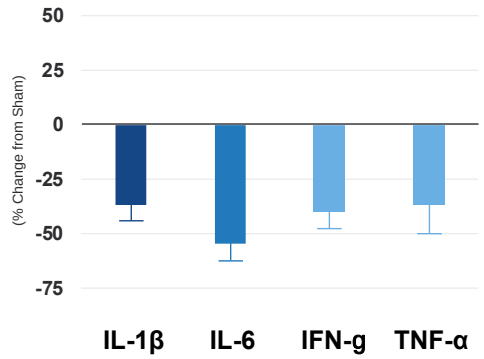
THERAPEUTIC APPLICATIONS OF STIMULATION

Electrical stimulation of the vagus nerve activates cholinergic anti-inflammatory pathway to reduces cytokine production

- Stimulation triggers intracellular signaling, which leads to inhibition of NF-kB activity, phosphorylation of JAK2-STAT3 and inhibition of inflammasome activation to induce suppression of multiple pro-inflammatory cytokines.

- Electrical stimulation of the vagus nerve downregulates a range of inflammatory cytokines by 30–70% and improves RA clinical disease activity measurements; while maintaining competent immune surveillance.



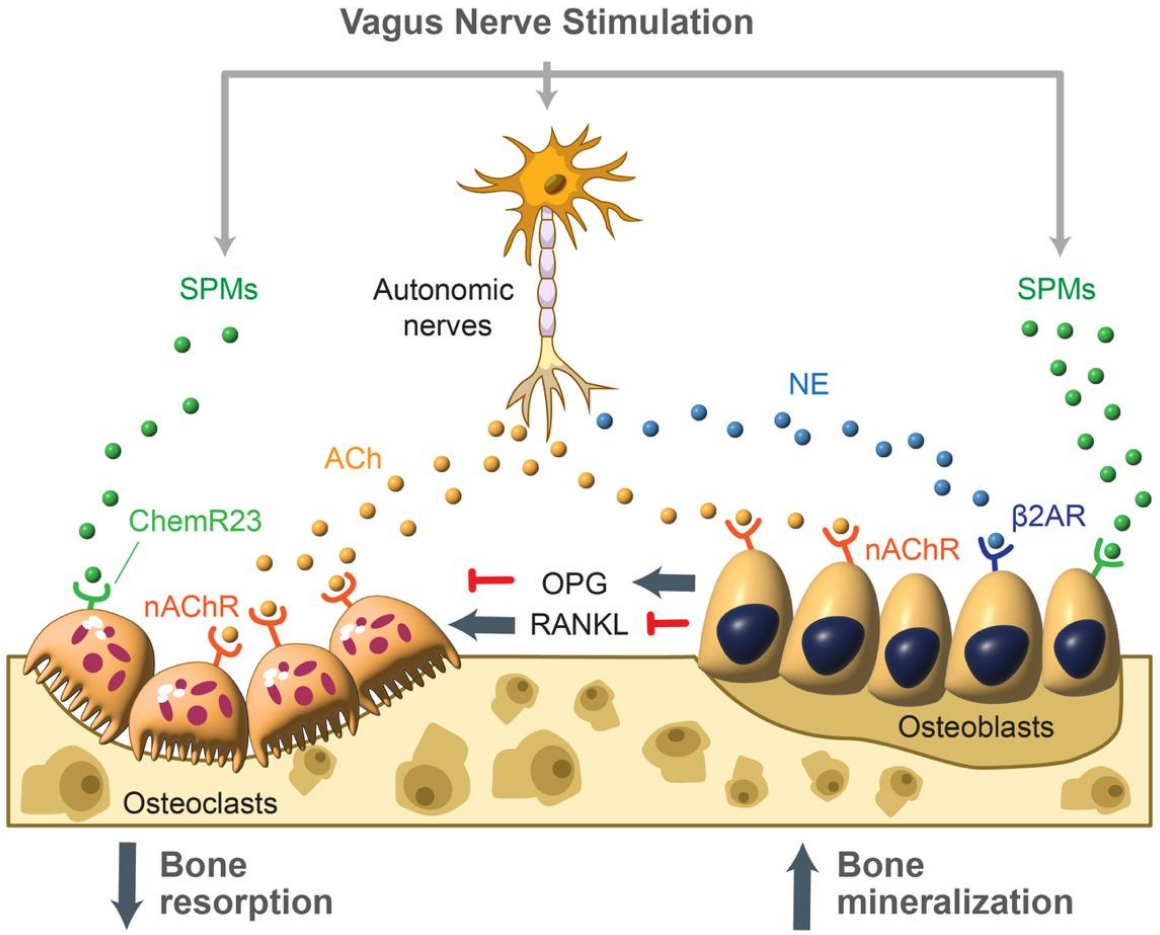


Nat. Rev. Rheumatol. 2009; 5: 229–232
PNAS 2016; 113:8284–8289
Frontiers in Immunol. 2018; 9:2648
J Intern Med. 2019; 286: 240–258
J Immunol. 2018; 201: 3161–3165
Immunity. 2017; 46(1): 92–105
Int. J. Mol. Sci. 2021; 22: 13427
PNAS. 2022; 117 (47) 29803-29810

VAGUS NERVE MEDIATED JOINT ACTIVITY

Electrical stimulation of the vagus nerve decreases bone resorption

- Vagus nerve stimulation mediated neurotransmitters and specialized pro-resolving mediators (SPMs) **increase bone mineralization** and decrease bone resorption.
- Vagotomy and nAChR knockout increase osteoclast activity and decrease bone mass.



PLoS One 2014; 9(8):e104530
Arth.& Rheum. 2009 60(5):1272-1281
J Intern Med. 2019 Sep;286(3):240-258

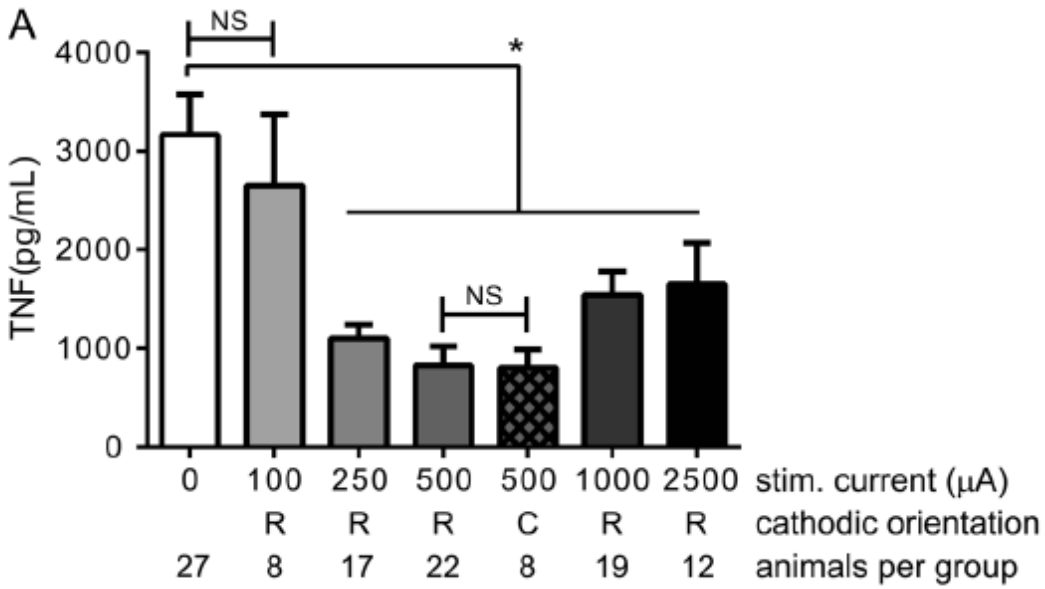
Eur J Oral Sci, 129(1), e12759
PNAS 2012 109(38): 15455-1546
Physiol Rev, 98(3), 1083-1112

TRANSLATIONAL RESEARCH

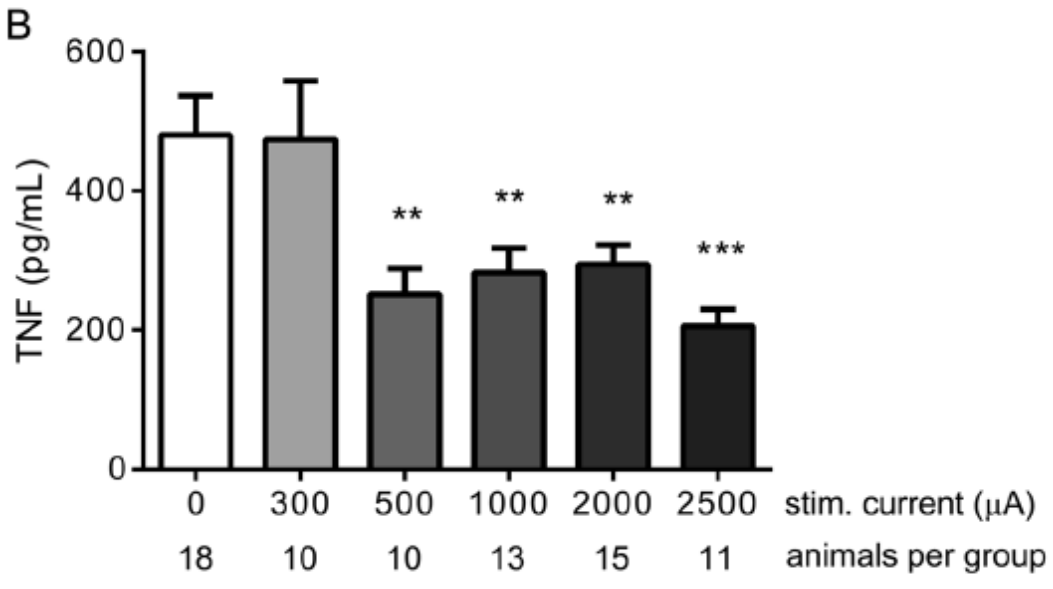
BIOMARKER DRIVEN OPTIMZATION OF STIMULATION

Stimulation current of ~500μA modulates TNF across species

Rats



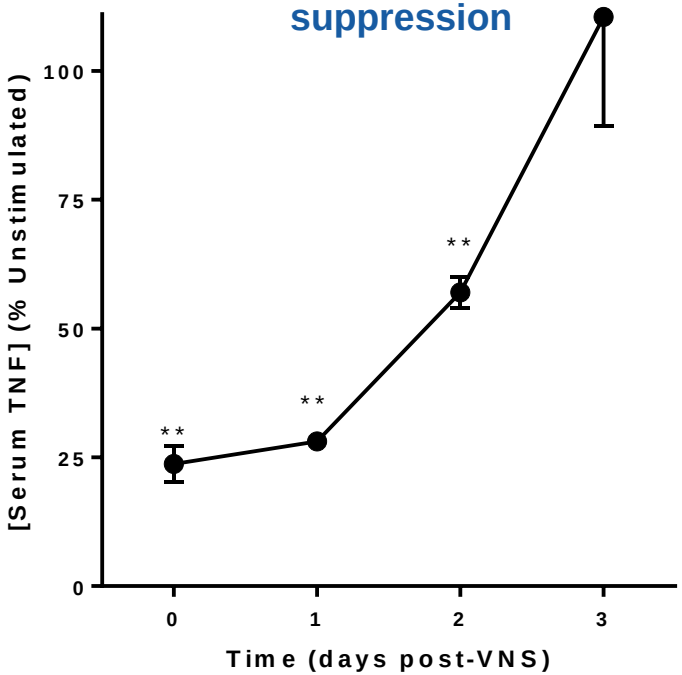
Mice



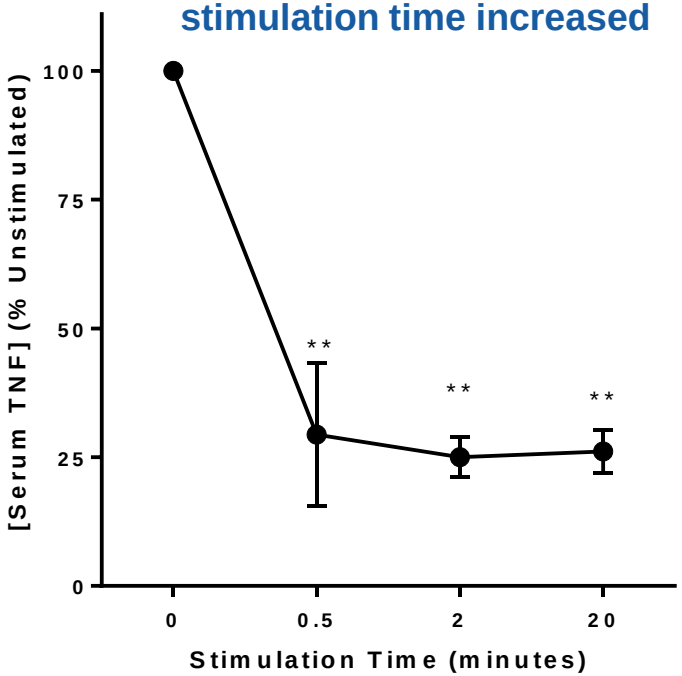
BIOMARKER DRIVEN OPTIMZATION OF STIMULATION

30 seconds of stimulation suppresses TNF for 48 hours

30s VNS results in 48h TNF suppression



Minimal benefit observed when stimulation time increased

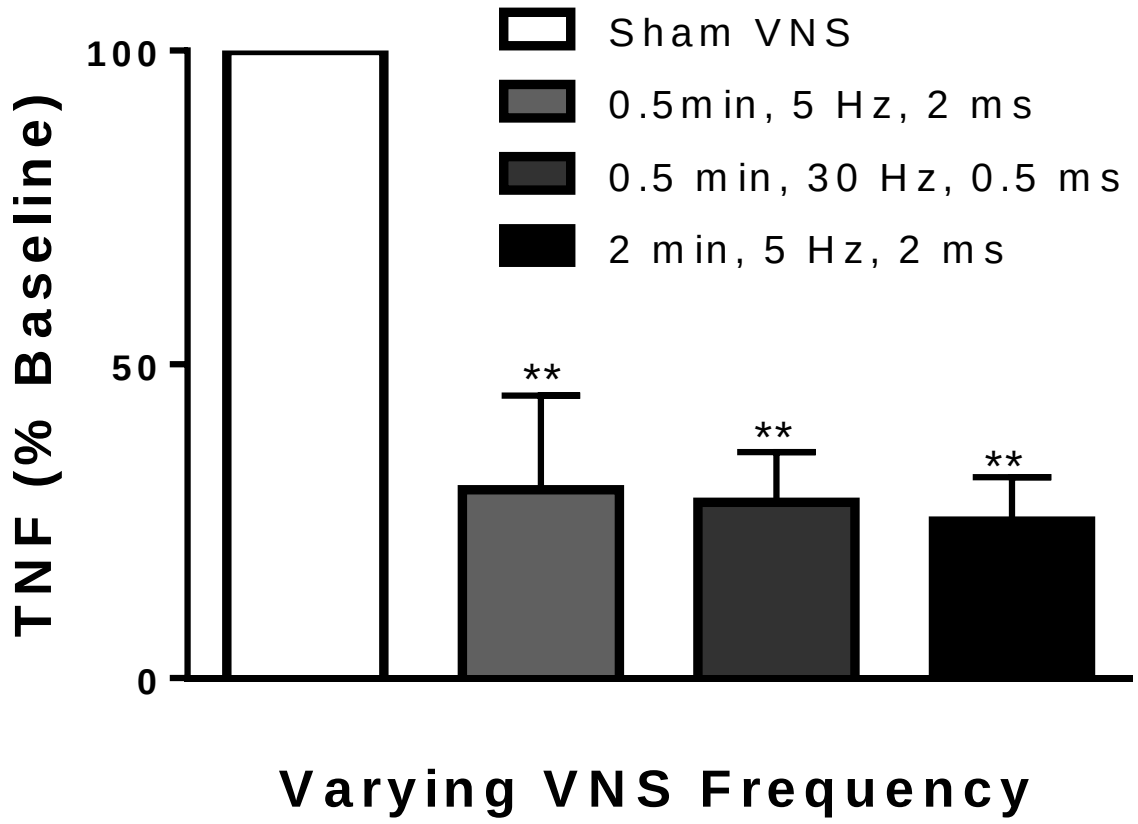


Implication: Therapeutic effect can likely be achieved chronically in humans with low duty cycle stimulation

Crit Care Med 2007; 35:2762

BIOMARKER DRIVEN OPTIMZATION OF STIMULATION

5-30 Hz showed TNF inhibition in mice

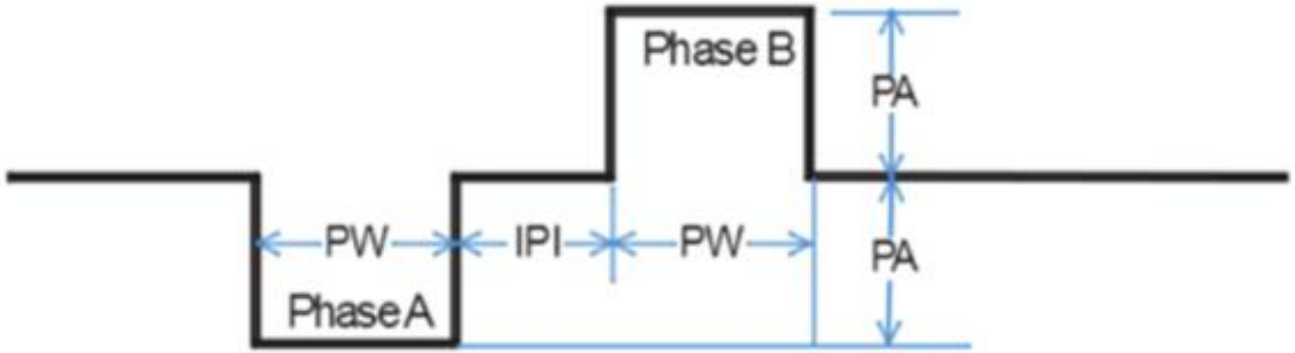


Crit Care Med 2007; 35:2762

BIOMARKER DRIVEN OPTIMIZATION OF STIMULATION

Preclinical research shaped parameters for clinical studies

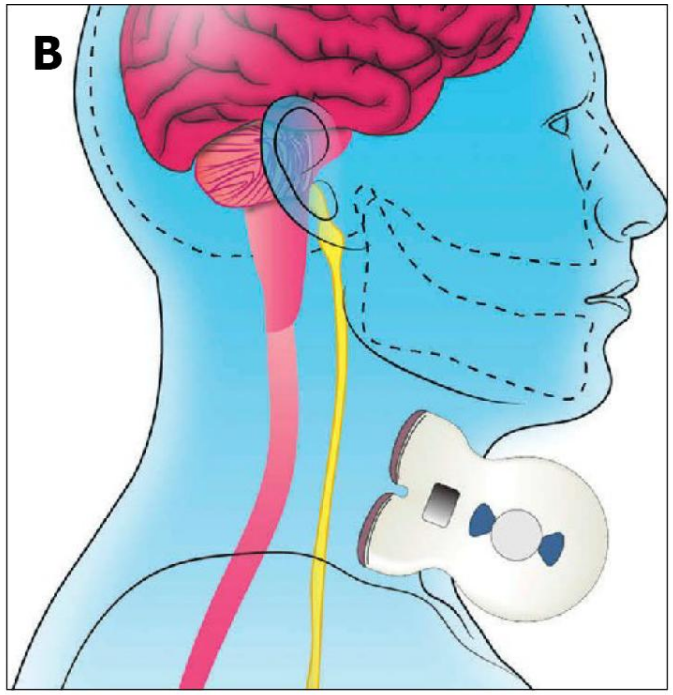
- Low duty cycle: 60 seconds/day
- Pulse Amplitude (PA): Titrate output current upward as tolerated, to maximum of 2.5 µA
- Pulse Frequency: 10 Hz
- Pulse Width (PW): 250 µsec
- Inter-Pulse-Interval (IPI): 0.05 ms
- Biomarkers confirmed activation of CAP



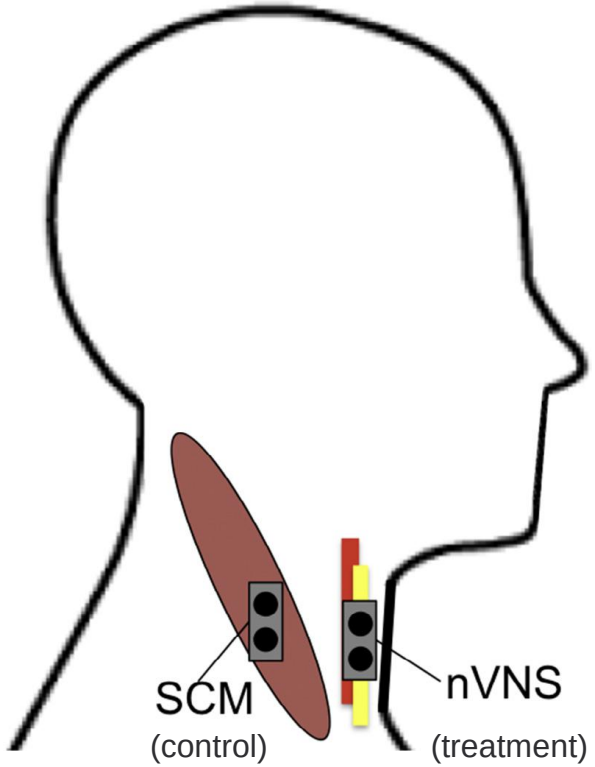
TRANSCUTANEOUS STIMULATION METHODS

TRANSCUTANEOUS VAGUS NERVE STIMULATION

External device placed over the neck to stimulate the vagus nerve



Transcutaneous vagus nerve stimulator



Stimulator placement on the neck

1. Brain Stimulation 10 (2017) 19–27
2. World J Gastrointest Pathophysiol. Sep 22, 2022; 13(5): 128-142

TRANSCUTANEOUS VAGUS NERVE STIMULATION STUDY

Preliminary proof-of-concept study highlights limited outcomes in the short term, with significant patient compliance challenges

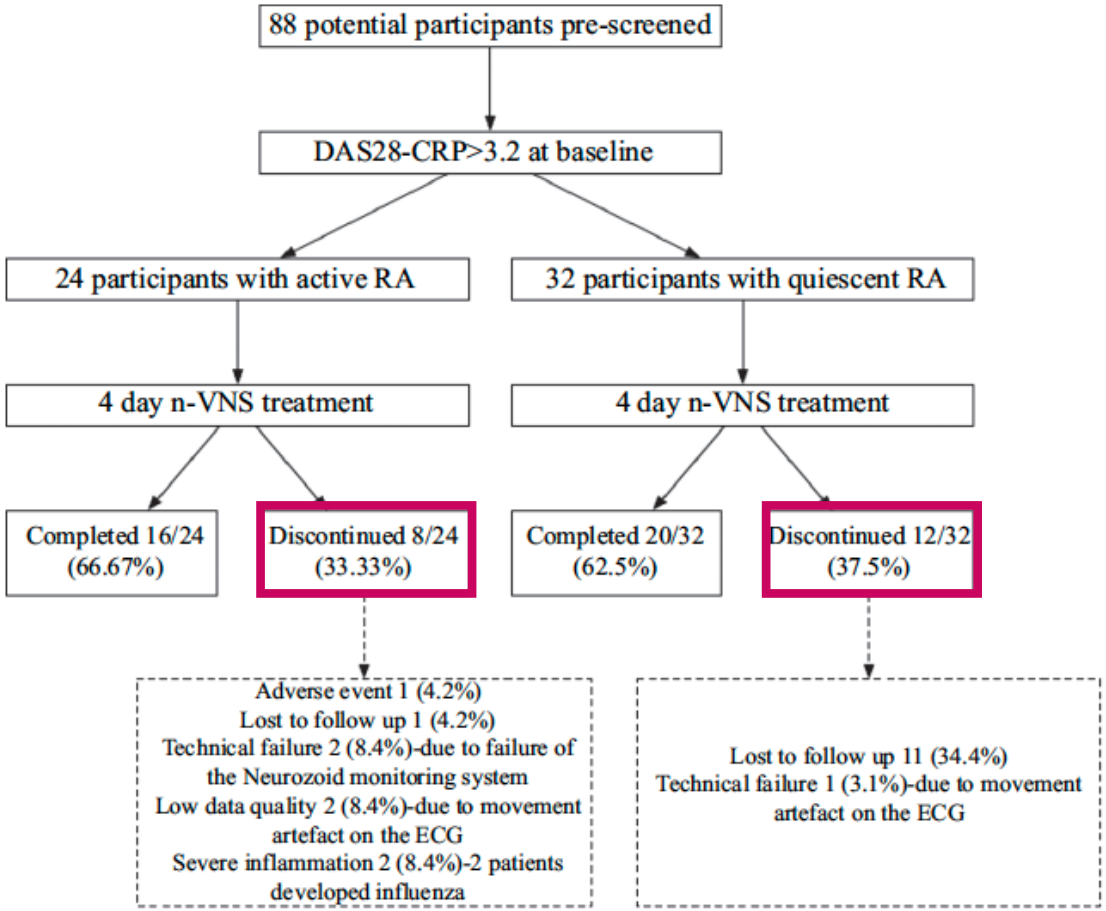


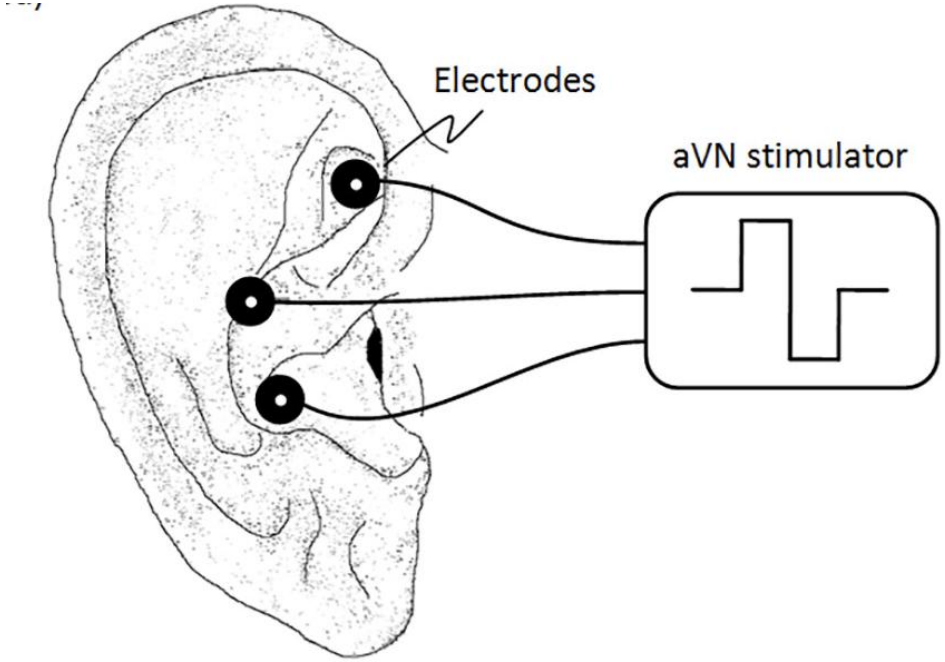
Table 2. Outcome measures at baseline and after 2 and 5 days, in participants with high rheumatoid arthritis disease activity.

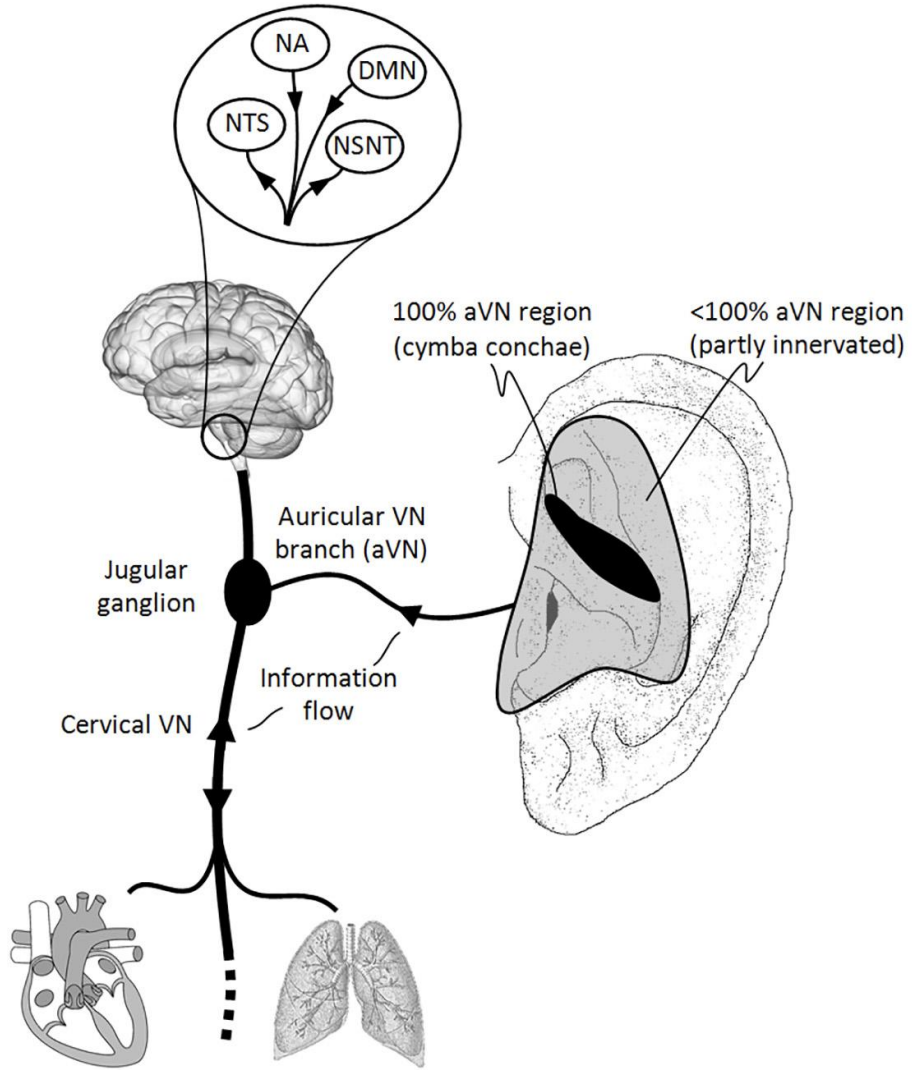
	Baseline	Day 2	Day 5	p
Cardiometric data				
CVT (LVS)	3.6 ± 2	3.7 ± 2	4.3 ± 2	0.62
HR (beats/min)	79 ± 11	78 ± 11	78 ± 12	0.63
Systolic BP (mmHg)	133 ± 18	126 ± 18	123 ± 19	0.004
Diastolic BP (mmHg)	81 ± 10	80 ± 10	78 ± 10	0.12
Disease activity				
DAS28-CRP	4.1 ± 1	3.7 ± 1	3.8 ± 1	0.02
CRP (mg/mL)	8.2 ± 11	8.6 ± 11	6 ± 7	0.01
Global VAS	54 ± 22	51 ± 23	53 ± 26	0.14
Swollen joints (number)	3.1 ± 2	2.6 ± 2	2.3 ± 2	0.05
Tender joints (number)	4.8 ± 2	3.4 ± 2	4.2 ± 3	0.07
Cytokines				
IL-6 (pg/mL)	4.7 ± 5	2.8 ± 3	4.6 ± 5	0.87
IL-8 (pg/mL)	6.3 ± 4	4.8 ± 2	5.4 ± 3	0.07
IL-10 (pg/mL)	0.9 ± 1	0.8 ± 1	0.8 ± 1	0.51
IFN12-p70 (pg/mL)	0.35 ± 0.2	0.35 ± 0.2	0.36 ± 0.2	0.83
IFN-γ (pg/mL)	29.8 ± 30	18.4 ± 16	22.5 ± 23	0.02
TNF-α (pg/mL)	11.4 ± 20	11.6 ± 20	11.7 ± 22	0.27

Scandinavian Journal of Rheumatology.2020 50(1), 20–27.

AURICULAR NERVE STIMULATION

Otic devices used to indirectly stimulate auricular branch of the vagus nerve

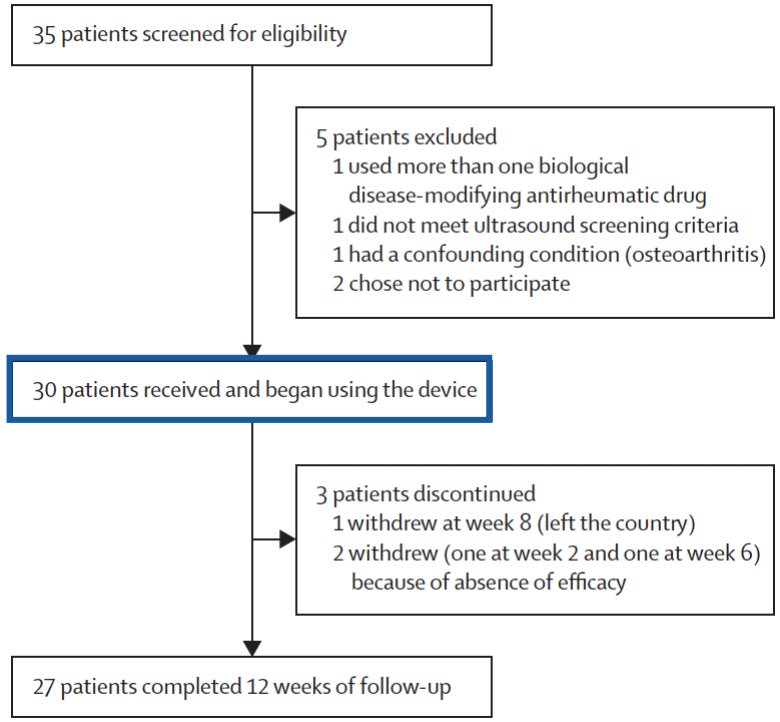


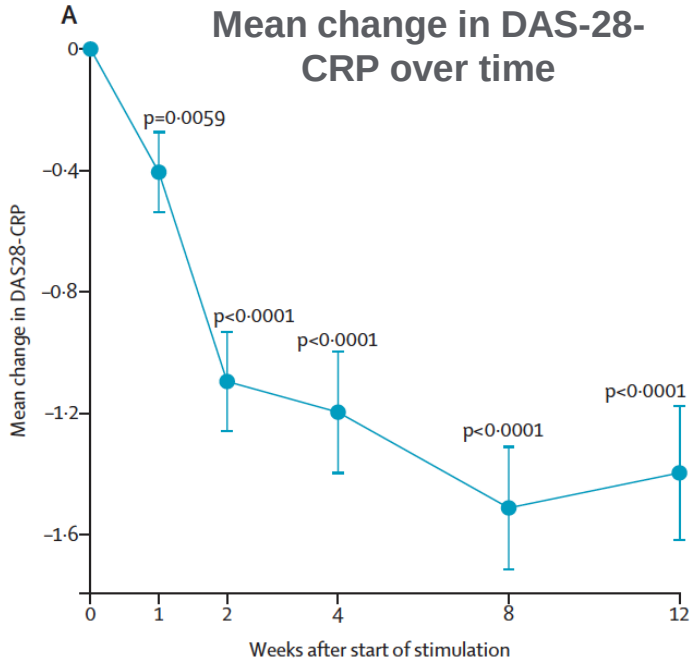


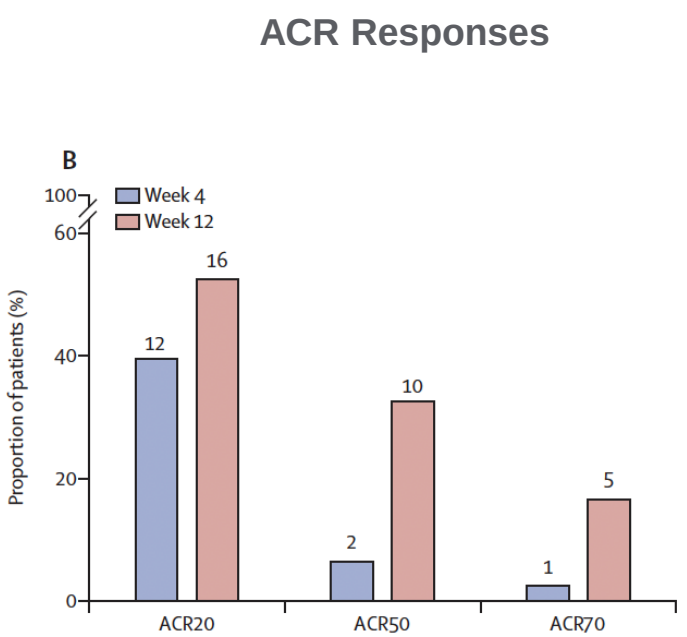
AURICULAR NERVE STIMULATION

Preliminary open-label, single-arm study showed clinical disease improvement in patients with RA

THE LANCET Rheumatology

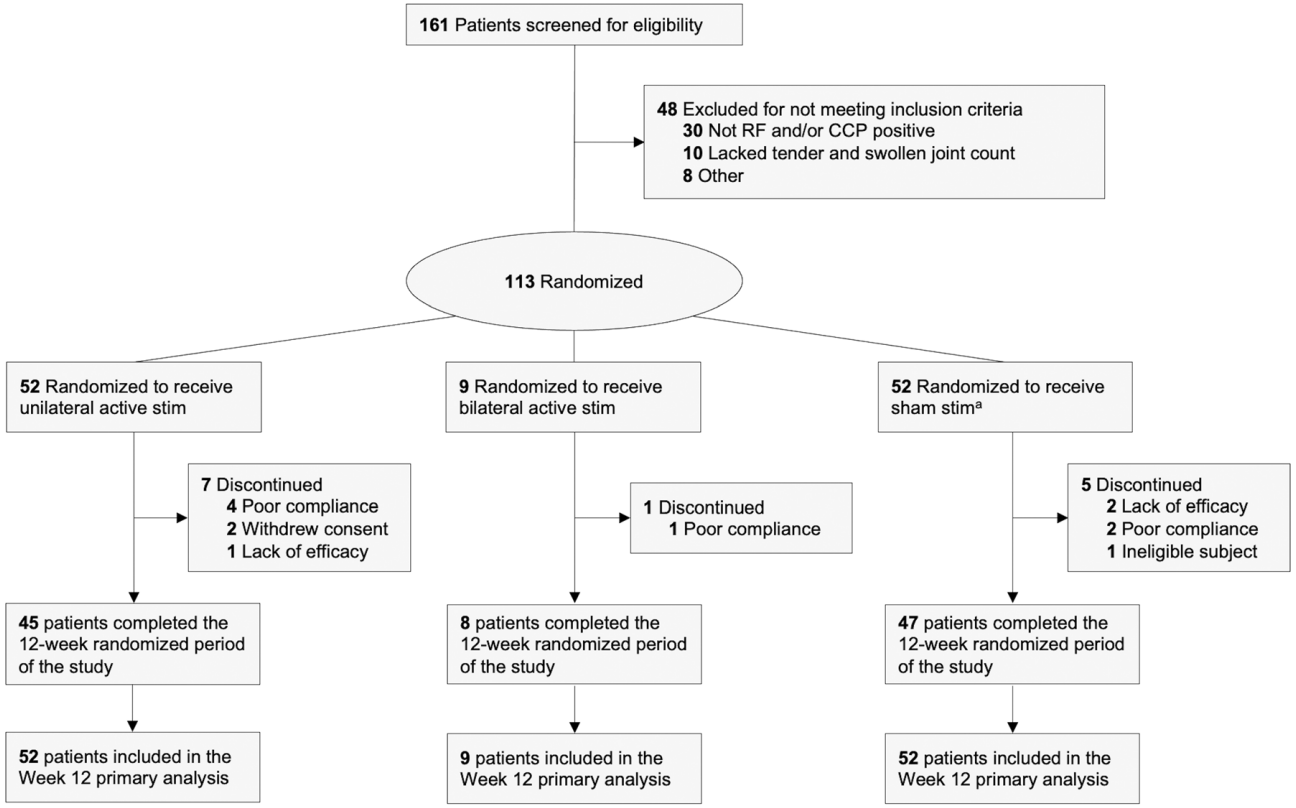


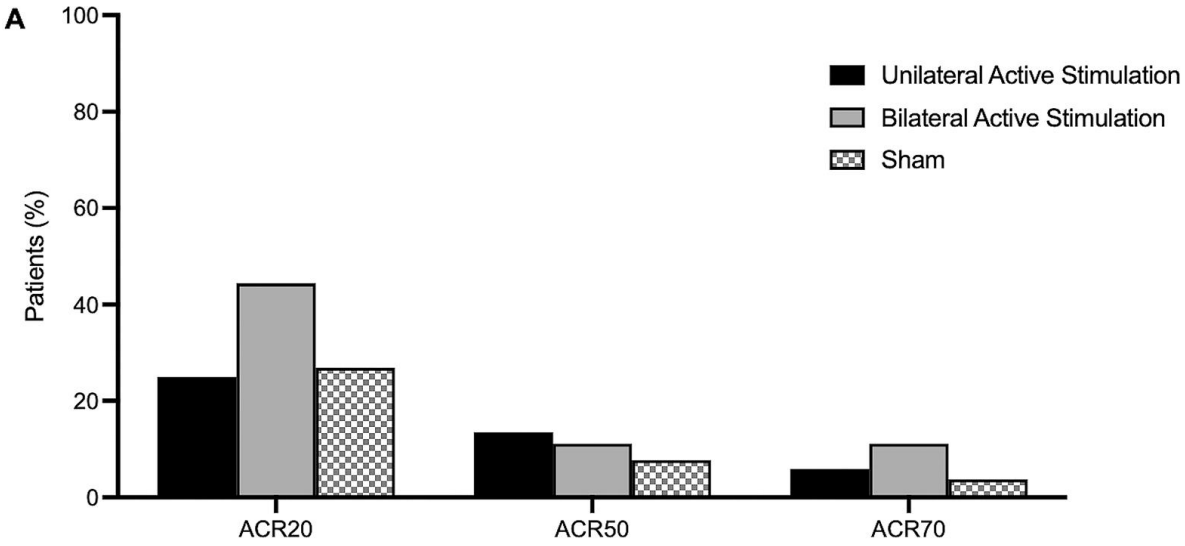




AURICULAR NERVE STIMULATION STUDY

Randomized, double-blind, sham-controlled clinical trial failed its primary endpoint and did not achieve a meaningful clinical response compared to sham



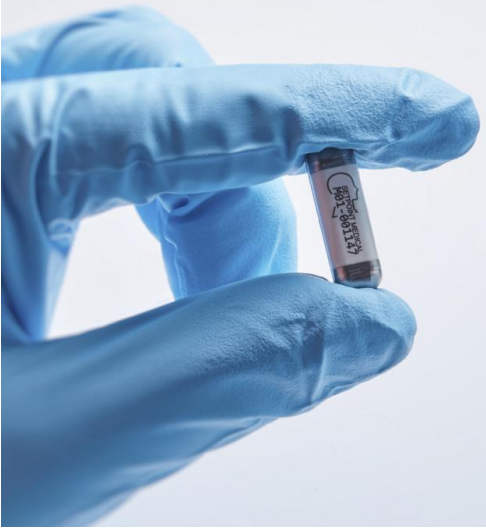


Arthritis & Rheumatology
Vol. 75, No. 12, December 2023, pp 2107–2115

DIRECT STIMULATION METHODS

DIRECT VAGUS NERVE STIMULATION

Integrated nerve stimulator designed to be placed on left cervical vagus



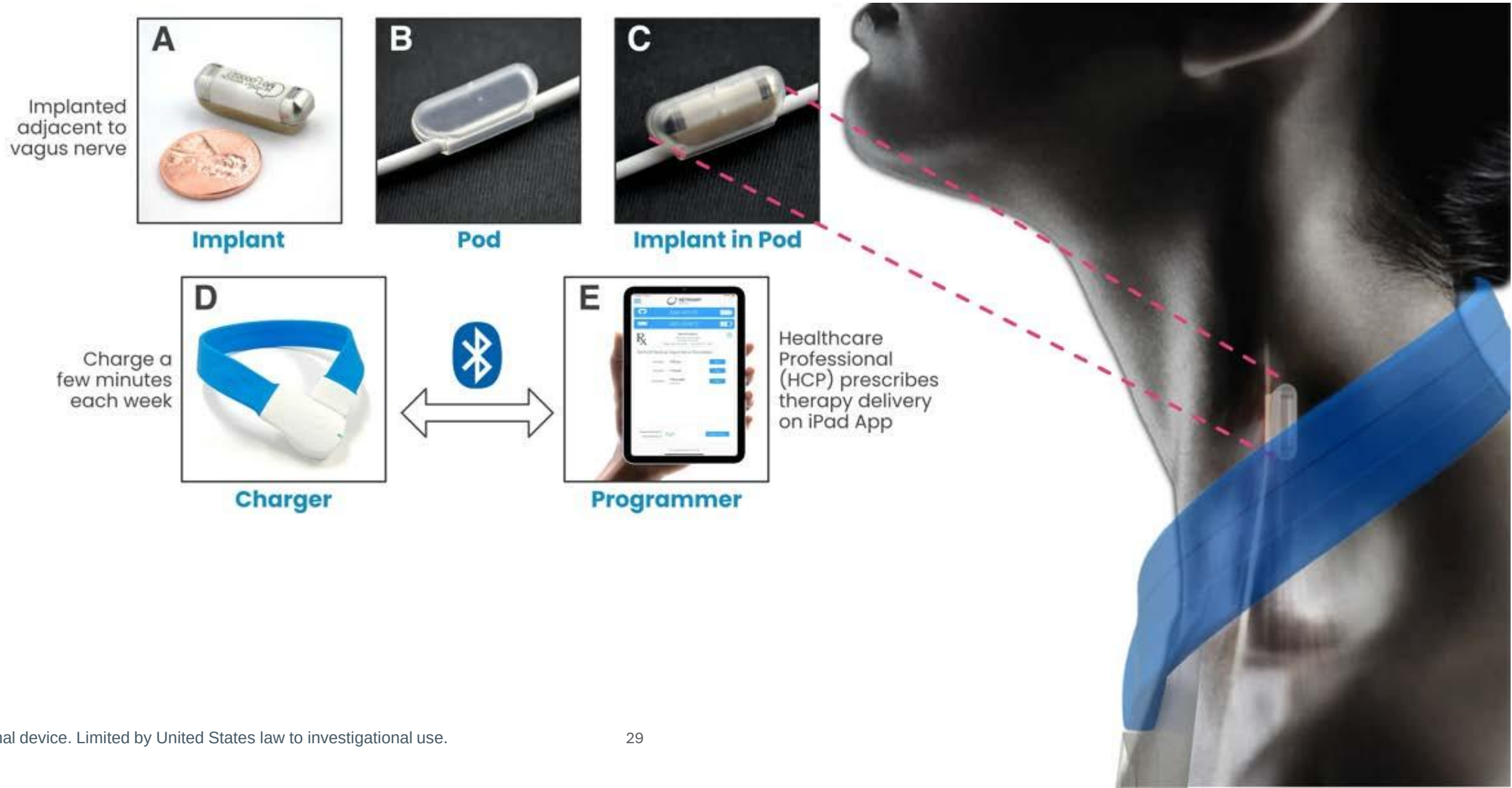
Small, rechargeable Implant
delivers 10 years of therapy after single implant procedure.

60-90 minute outpatient procedure
performed by neurosurgeon under general anesthesia.

Once activated by rheumatologist, **automatic therapy is delivered** daily.

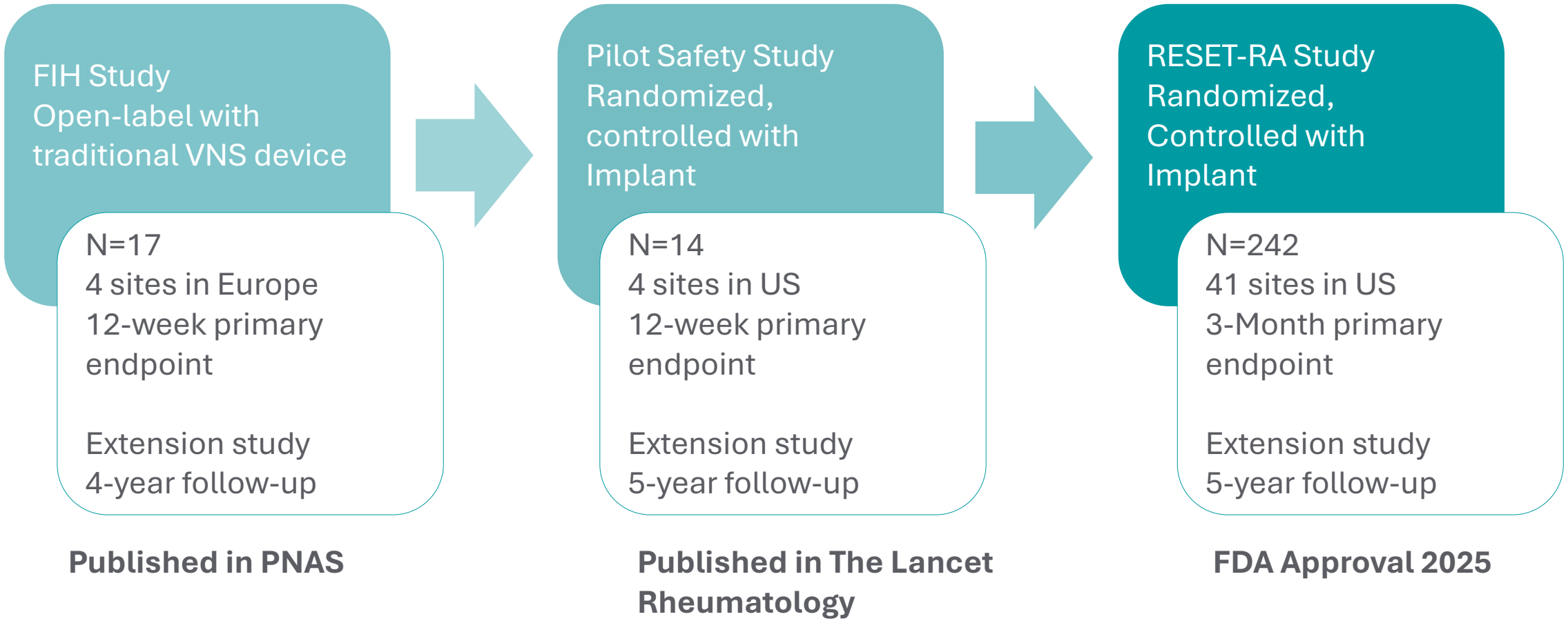
DIRECT VAGUS NERVE STIMULATION

Integrated nerve stimulator designed to be placed on left cervical vagus



DIRECT VAGUS NERVE STIMULATION

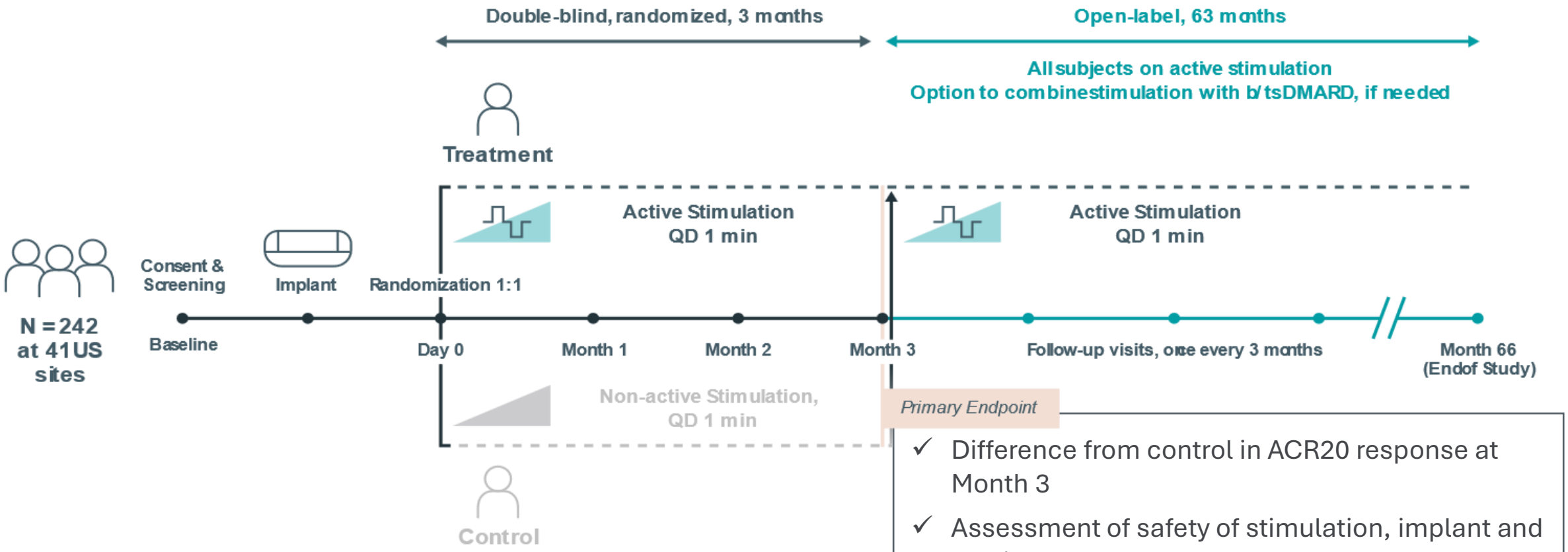
Clinical development



[1] PNAS 113:8284-9 (2016)
[2] Lancet Rheumatol. S2665-9913(20)30172-7 (2020)

RESET-RA: STUDY DESIGN

Randomized, sham-controlled, double-blind study in RA patients who have inadequate response, loss of response, or intolerance to at least 1 b/tsDMARDs



RESET-RA: DEMOGRAPHICS SLIDES

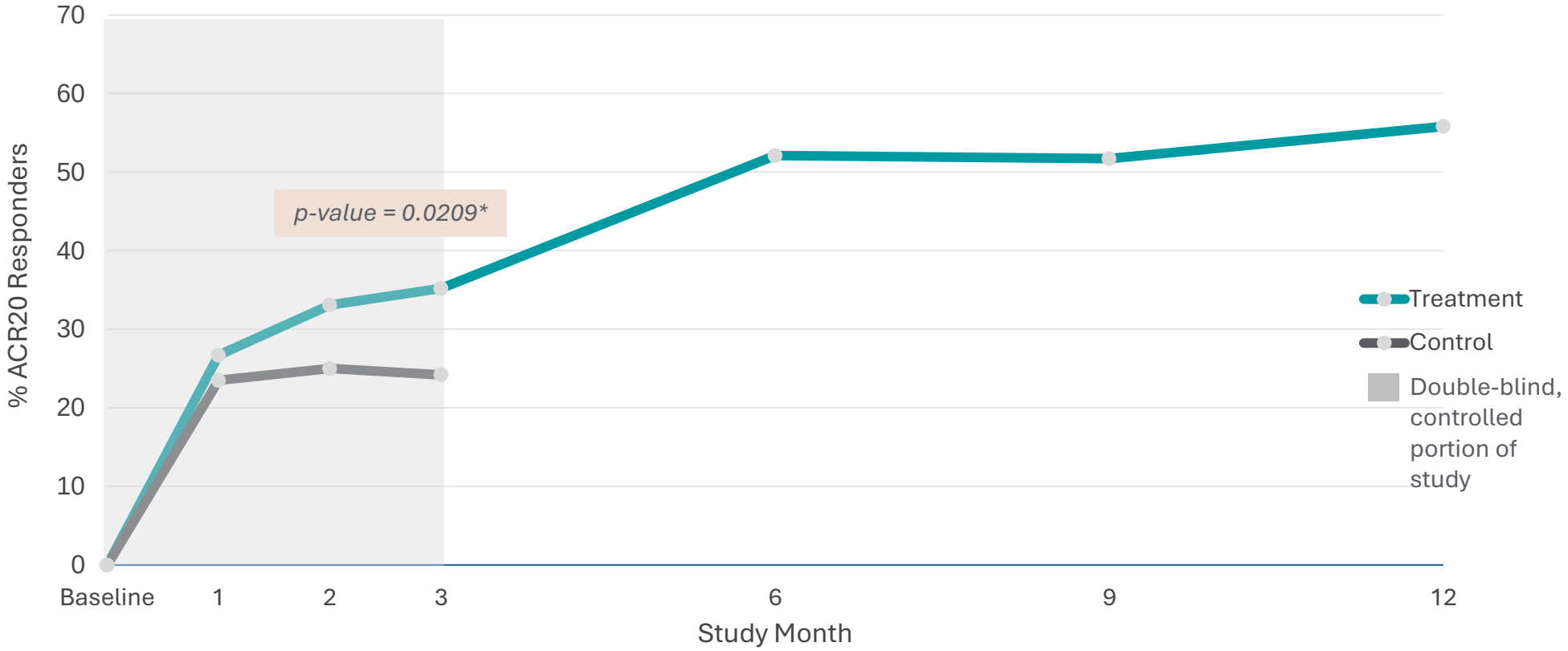
Demographics were representative of a real-world U.S. RA population

	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 (21.1%)
Leflunomide	17 (14.2%)	10 (8.2%)
Sulfasalazine	4 (3.3%)	4 (3.3%)
Combination	23 (19.2%)	29 (23.8%)

	Control (N=120)	Treatment (N=122)
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%)
Prior b/tsDMARDs by category		
Anti-TNF	109 (90.8%)	116 (95.1%)
Anti-IL-6	28 (23.3%)	27 (22.1%)
JAK inhibitor	24 (20.0%)	25 (20.5%)
CTLA4-Ig	36 (30.0%)	32 (26.2%)
B-cell depleting	21 (17.5%)	13 (10.7%)
Anti-IL-1	4 (3.3%)	0 (0.0%)

RESET-RA: PRIMARY ENDPOINT

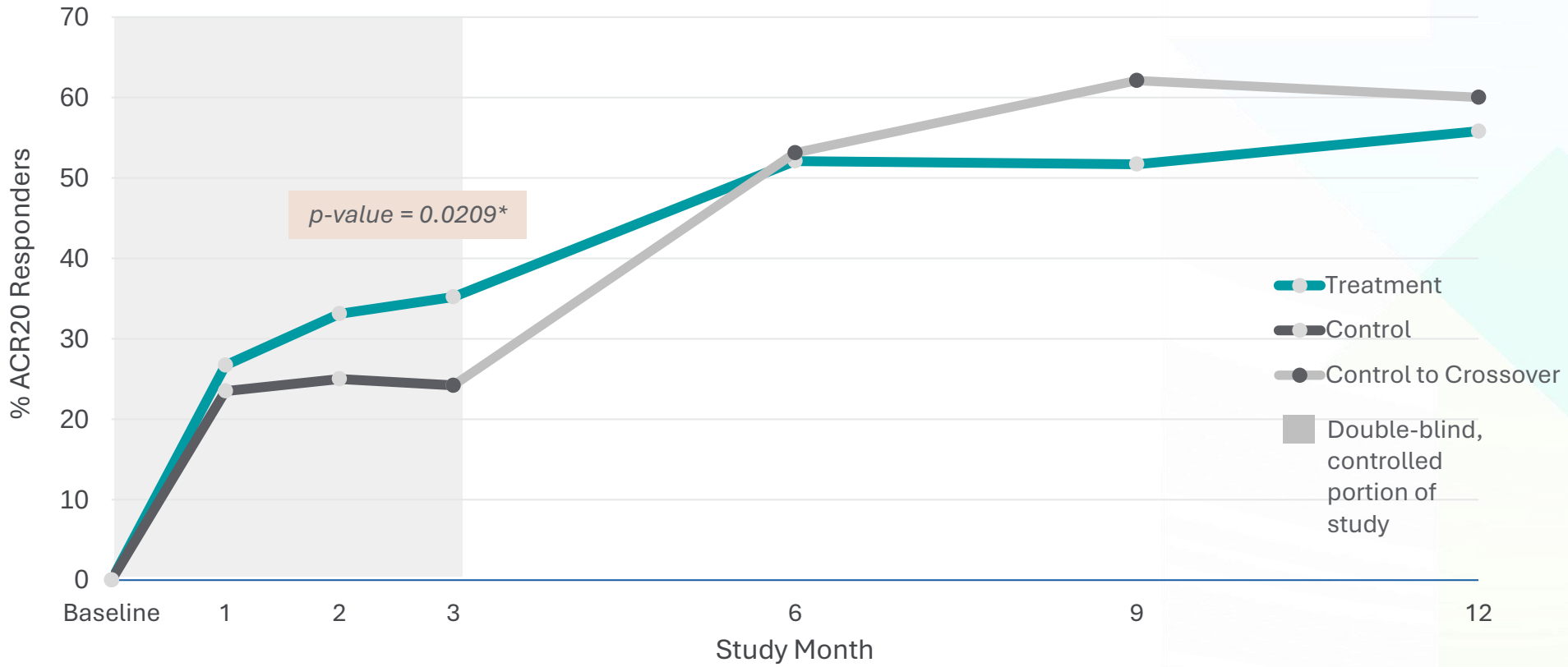
Study met primary endpoint of ACR20 at 3 months



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 stimulation monotherapy, i.e. excludes data from patients if stimulation treatment was combined with high-dose steroid or b/tsDMARD

RESET-RA: PRIMARY ENDPOINT

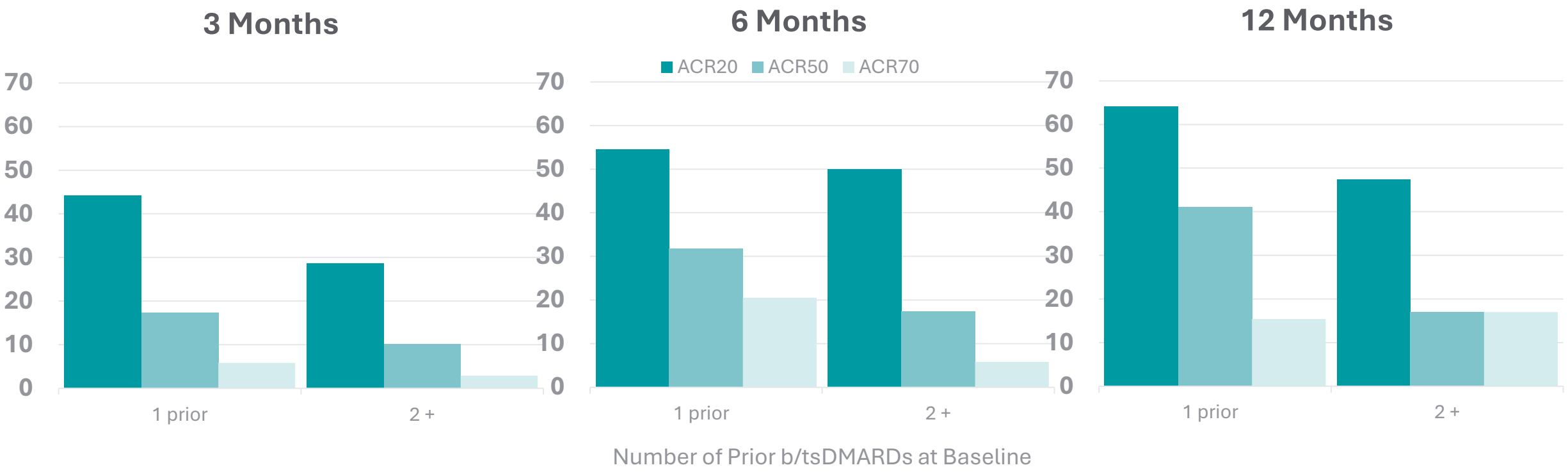
Study met primary endpoint of ACR20 at 3 months



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 stimulation monotherapy, i.e. excludes data from patients if stimulation treatment was combined with high-dose steroid or b/tsDMARD

RESET-RA: ACR RESPONSES

Prespecified analysis of ACR20/50/70 responses for Treatment group by prior b/tsDMARD use



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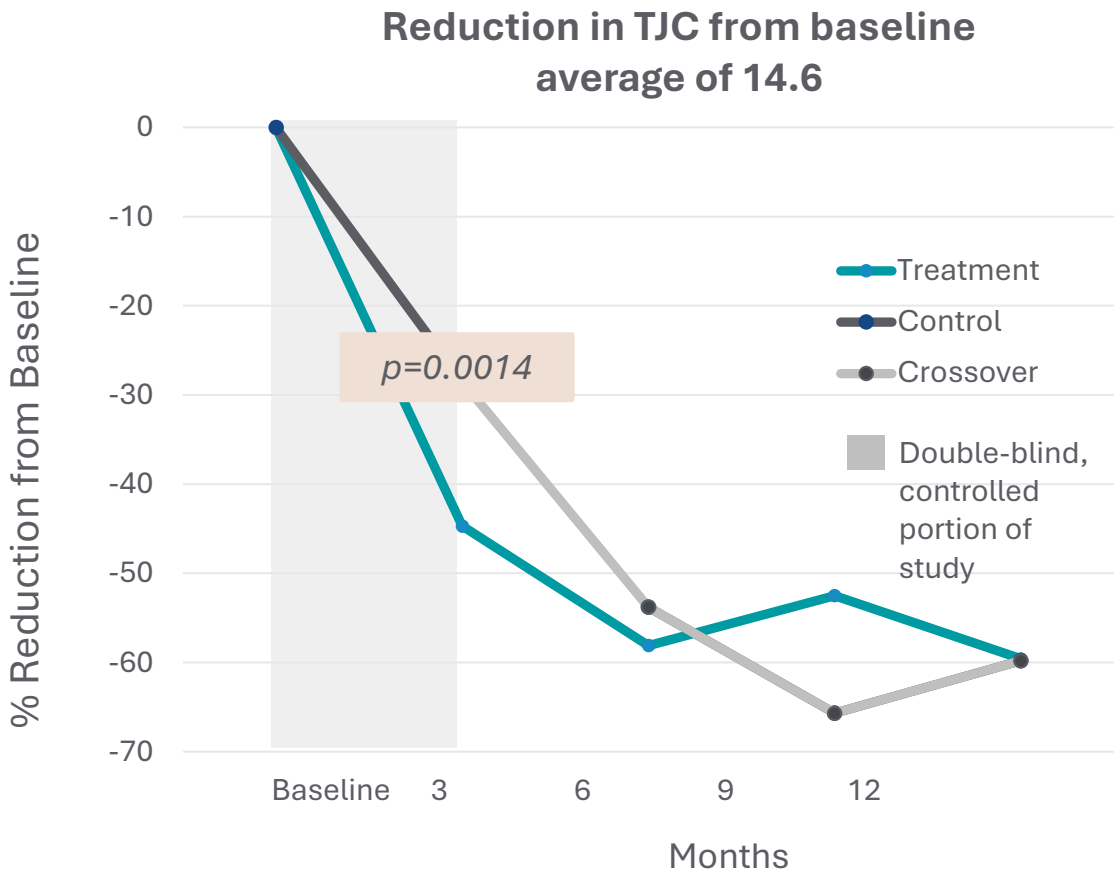
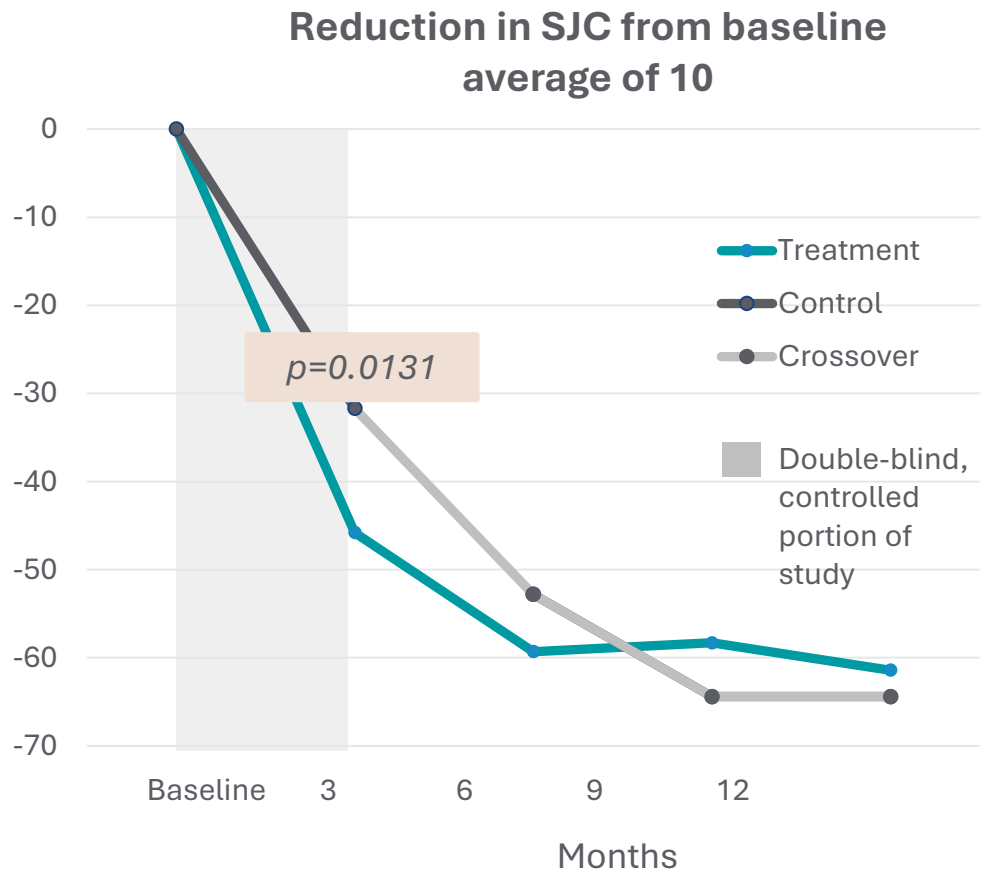
RESET-RA: TENDER AND SWOLLEN JOINT COUNTS

Statistically significant improvements observed in joint counts which continue to improve through 12 months of neuroimmune modulation





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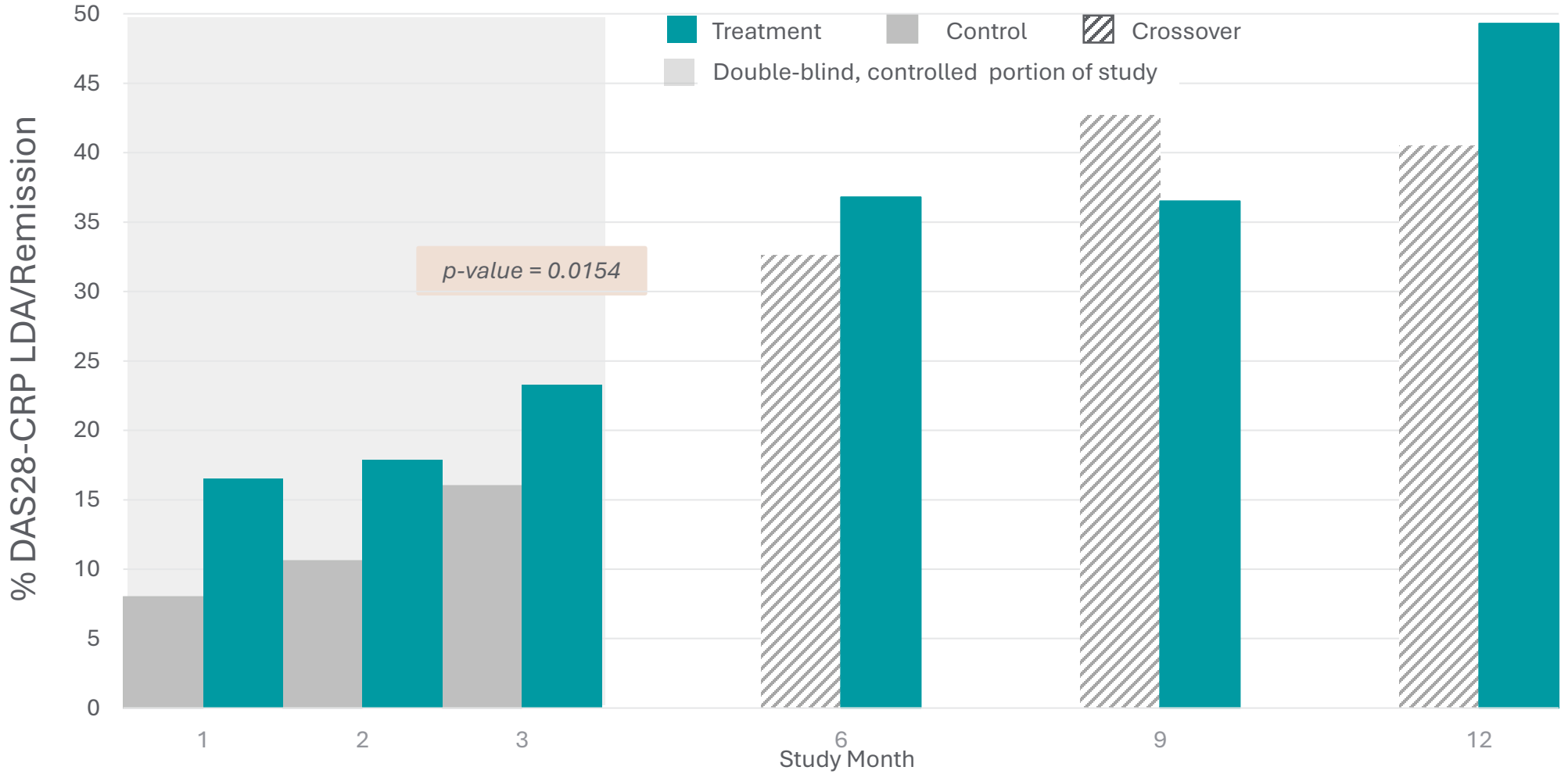
RESET-RA: DISEASE ACTIVITY

DAS28-CRP LDA/remission rates through 12 months



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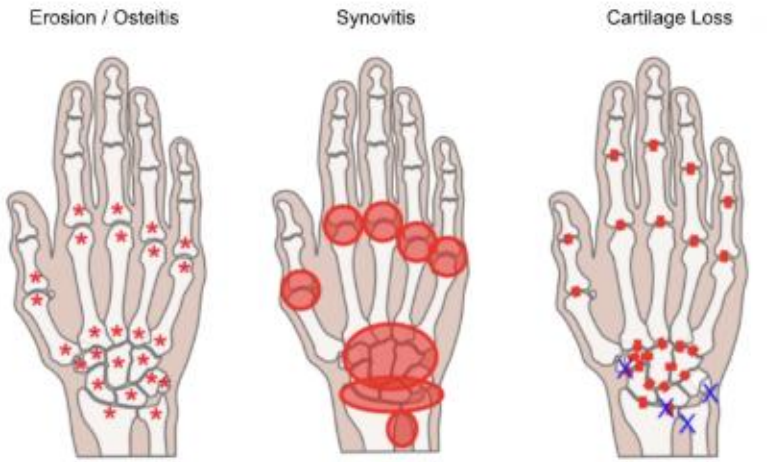
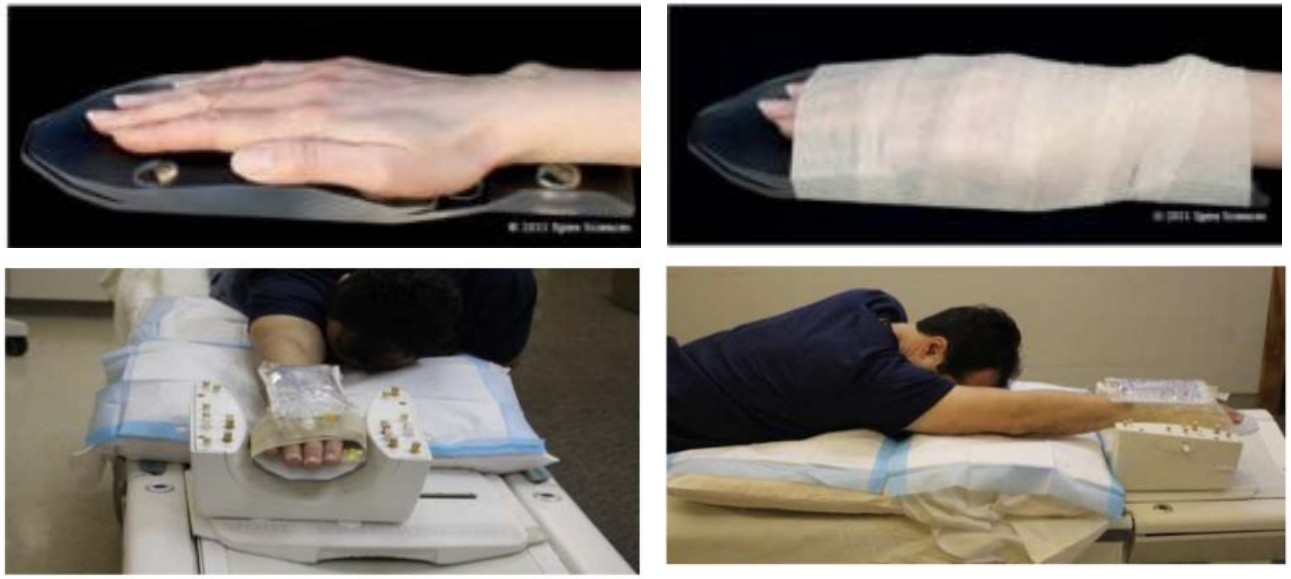
RAMRIS ANALYSIS USING Gd-ENHANCED MRIs

RAMRIS data at 3 months is indicative of radiographic progression with X-rays seen at 12 months

- RAMRIS evaluates erosions, osteitis, and synovitis across 23 joints in the hand and wrist
- More sensitive imaging allows scans can be evaluated sooner than what is typical with x-rays
- 3-month RAMRIS data is equivalent to x-ray data at 12 months



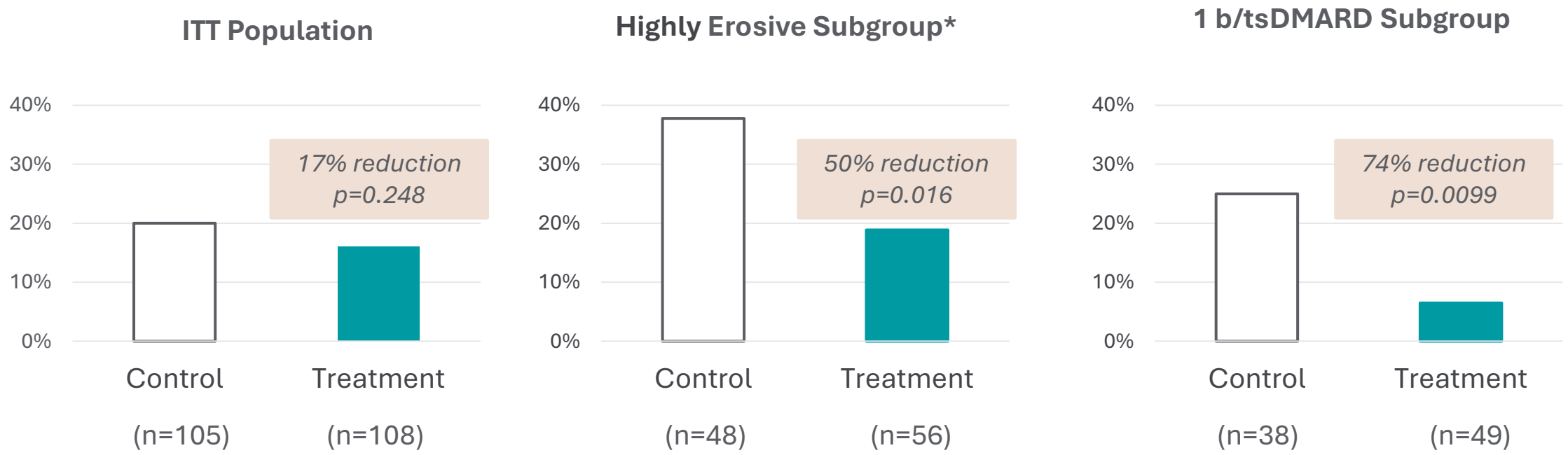


*Erosive Subgroup: Baseline synovitis score of 2 or more on any joint; or -if none of the joints score greater than 1, having at least 4 joints with a score of 1 at baseline; or -having any joint with osteitis at baseline

1. Ann Rheum Dis. 2014 Nov;73(11):1968-74.

STRUCTURAL JOINT PROTECTION BY RAMRIS

Neuroimmune modulation is effective in reducing the progression of structural damage as early as 3 months



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RESET-RA: SAFETY

1.65% related SAE risk in first 12 weeks; all known risks associated with vagus nerve procedures. Risks are typically transient and resolve over time

	Through Month 3 (Blinded Period)	
	Treatment N=122	Control N=120
Number of pts (%) with Adverse Event	81 (66.4%)	86 (71.7%)
Procedure or Device Related*	16 (13.1%)	22 (18.3%)
Stimulation Related*	10 (8.2%)	0
Serious Adverse Events	4 (3.3%)	5 (4.2%)
Related, Serious Adverse Event[3]	3 (2.5%)	1 (0.8%)
Unrelated, Serious Adverse Event	2 (1.6%)	4 (3.3%)
Serious Infection (unrelated)	0	1 (0.8%)
AE Leading to Study Discontinuation	0	0
Death	0	0

Consistent with safety of other vagus nerve stimulation devices spanning decades of use and 150,000 implants in non-autoimmune disease populations

RESET-RA: LONG TERM SAFETY

No new, related SAEs in long-term follow-up through 12 months; no serious infections, malignancies, or cardiac events associated with SetPoint Therapy through 12 months

	Through Month 12	
	Treatment N=121	Crossover N=120
Number of pts (%) with Adverse Event	84 (69.4%)	88 (73.3%)
Procedure or Device Related*	1 (0.8%)	2 (1.7%)
Stimulation Related*	4 (3.3%)	5 (4.2%)
Serious Adverse Events	7 (5.8%)	14 (11.7%)
Related, Serious Adverse Event[3]	0	0
Unrelated, Serious Adverse Event	7 (5.8%)	14 (11.7%)
Serious Infection (unrelated)	0	5 (4.2%)
AE Leading to Study Discontinuation	0	1 (0.8%)
Death	0	0

Study protocol allowed combining biologics or JAKs with SetPoint Therapy.

Only 25% of patients were on combined therapy at 12 months

SUMMARY

- Excessive inflammation driven by autoimmune pathology drives the clinical manifestations, damage and functional loss of RA
- Vagus nerve mediated mechanisms play a critical role in maintaining inflammatory homeostasis.
- Neuroimmune modulation can be used to activate innate reflexes; reducing inflammation and coordinating immuno-resolution.
- Several devices with varying techniques are being evaluated for the use in patients with autoimmune conditions like RA.
- RESET-RA study evaluating an implantable vagus nerve stimulator successfully met its safety and efficacy endpoints for treatment of biologic-experienced RA
- Neuroimmune modulation represent a novel therapeutic option for treatment of RA.