

A Single Arm Pilot Study to Evaluate the Safety, Feasibility, and Dose Ranging of Splenic Nerve Stimulation in Patients with Rheumatoid Arthritis Using a Novel Implantable Device

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Abstract

Background:

Preclinical studies have demonstrated that splenic nerve stimulation (SpNS) can effectively modulate immune responses and reduce inflammation. This open-label single arm study was conducted to evaluate the safety and feasibility of SpNS with an active implantable neuromodulation device in patients with rheumatoid arthritis (RA).

Methods:

RA patients who had inadequate responses to two or more biologic or targeted synthetic disease-modifying anti-rheumatic drugs (b/ts)DMARDs were laparoscopically implanted with the device. Prior to implantation, a washout of b/tsDMARDs was performed, but participants were allowed to stay on a stable dose of conventional synthetic (cs)DMARD or low dose oral prednisone. After a recovery for a period of approximately 28 days, SpNS was initiated for 12 weeks, followed by continued stimulation during the long-term follow-up period with or without a b/tsDMARD. The primary outcome measures were the safety and tolerability of the device, its implantation, and chronic SpNS. Secondary and exploratory outcome measures included changes in disease activity and in blood biomarkers. In addition, stimulation dose ranging was evaluated.

Results:

Five patients were enrolled in the study. The device was successfully implanted in all participants and subsequently programmed to deliver SpNS. No serious or unanticipated adverse effects related to the implantation, stimulation or device were observed. In one participant, the stimulation was stopped after 12 weeks due to a Device Deficiency (DD). Stimulation was generally well tolerated in all participants, when delivered 6 or 12 times per day, as well as during day and night. One participant demonstrated a marked reduction of DAS28-CRP of -2.34 at week 12, which was accompanied by a drug free remission of a pre-existing refractory complex regional pain syndrome type 1 (CRPS-1). In this participant a reduction in pro-inflammatory cytokines was observed, especially IL-17A. This was accompanied by a reduced STAT3 phosphorylation in Th17 cells.

Conclusion:

This first single arm open-label clinical trial evaluating a new investigational implantable neuromodulation device demonstrated that implantation and SpNS was feasible, demonstrated a favourable safety profile, and was well tolerated. Additionally, a reduction in RA disease activity was observed in one participant receiving stimulation in combination with a csDMARD for more than 1.5 years and this was accompanied by a remarkable reduction in pain caused by CRPS-1. In addition, one participant receiving a combination of a tsDMARD and stimulation in Period 2 exhibited clinically meaningful reductions in disease activity. Together, these findings warrant future studies in larger patient groups to determine if SpNS is a valuable novel treatment option for patients with RA.

Trial registration

Clinicaltrial.gov NCT04955899, 5th of July 2021

INTRODUCTION

Over the last three decades, the therapeutic options for RA treatment have increased significantly. The use of disease-modifying antirheumatic drugs (DMARDs), from conventional synthetic (cs) DMARDs to biologic and targeted synthetic (b/ts)DMARDs, has improved clinical outcomes and patient quality of life [1]. The current therapeutic approach emphasises

rapid induction of treatment to achieve remission or low disease activity (LDA) with regular evaluation and treatment adjustment in a 'treat-to-target' manner [2]. Despite these advances, RA remains difficult to manage for a substantial number of patients with partial- or no-response to multiple lines of therapy together with medication-related adverse events leading to failure to achieve remission or LDA [3]. This subset of RA patients has been categorised as 'difficult-to-treat' (D2T) RA [4]. Moreover, the focus of the current treatments is on a reduction in disease activity, while reduction in pain remains a major challenge in RA. This highlights the need for continued innovation in treatment strategies for RA.

The field of neuromodulation, using electrical impulses to alter nerve activity and influence physiological processes, holds potential to provide novel treatment benefits, including the modulation of inflammatory pathways and immune responses [5]. Vagus nerve stimulation (VNS) has been investigated as a method for reducing systemic inflammation with promising results reported in clinical trials of RA, osteoarthritis and inflammatory bowel disease [6–10] and recently received FDA approval as a therapy in patients with moderate to severe RA [8]. However, since the vagus nerve innervates multiple organs, off-target effects can occur, particularly with cervical vagus nerve stimulation [11]. Such off-target effects limit maximally tolerable stimulation levels and, consequently, may ultimately limit therapeutic efficacy.

VNS evokes post-synaptic neural responses in the splenic nerve via the celiac ganglion, activating sympathetic adrenergic neurons projecting to the spleen [12]. The spleen has been shown to play a principal role in the neural regulation of systemic inflammation [13, 14]. The therapeutic potential and safety of SpNS have been demonstrated in preclinical disease models [15–18]. In *in vivo* mice and pig models, stimulation of the splenic nerve led to noradrenaline (NA) release in the spleen. In such *in vivo* models as well as and in an *in vitro* model of human splenocytes, noradrenaline was shown to bind to adrenergic receptors reducing serum TNF α , IL-6, kynurenines, and the number of pro-inflammatory monocytes in the spleen. In mouse models of RA, initiation of SpNS *after* disease-onset showed significant reduction in clinical scores and reduction in pro-inflammatory cytokines [15]. Importantly, SpNS suppressed LPS-induced inflammation in pigs implanted with the device and treated with the dosing strategy developed for human clinical use [17]. In pigs, a decrease in pro-inflammatory cytokines and monocytes was observed while specialised pro-resolving mediators such as resolvins and protectins were increased [18]. Physiological measurements and histopathological assessments revealed preservation of the functional and histological integrity of the splenic nerves up to 70-day post implantation in these pigs. A feasibility study in patients undergoing minimal invasive esophagectomy (MIE) demonstrated for the first time in humans that applying a cuff around the splenic neurovascular bundle (NVB) and subsequent stimulation was safe and feasible during surgery. Moreover, SpNS showed an effect on the postoperative inflammatory response following MIE, as was demonstrated by a decrease in C-reactive protein (CRP) post-surgery in patients treated in the trial compared to a historical control group [19].

Taken together, we hypothesise that SpNS with an implantable device in patients with RA could provide robust and reliable activation of the splenic nerve, to evoke downstream immunomodulatory effects which are different from ones achieved by currently available therapeutic options. Here we present the first open-label study with an investigational implantable neuromodulation device delivering chronic SpNS in D2T RA patients to evaluate feasibility, safety, tolerability, dose ranging and preliminary efficacy. We also discuss the unexpected positive effect on a preexisting complex regional pain syndrome type 1 (CRPS-1) observed in one of the participants.

PATIENTS AND METHODS

Study design

An open-label, single arm, early feasibility phase 1b trial was conducted in five patients with active RA evaluating the safety, feasibility, and tolerability of stimulating the NVB with an investigational active implantable medical device, the Galvani System. The study was executed at three sites; the Greater Glasgow and Clyde Health Board (GGCHB), Scotland, the Amsterdam University Medical Centre (Amsterdam UMC), the Netherlands, and the Catharina Hospital, Eindhoven, the Netherlands. The study consisted of screening, implant and recovery, and a 12-week Open-Label SpNS period (Period 1), followed by a 5-year long-term follow up (LTFU, Period 2). Figure 1 shows a schematic timeline of the overall trial design. Full study protocol is provided in the supplementary file (S1).

Study Participants

Patients aged 22–75 years were eligible if diagnosed with RA according to the ACR/EULAR 2010 criteria and having moderate-to-severe RA defined as having at least three swollen joints, a DAS28-CRP > 3.2, and/or CRP ≥ 15.0 mg/L. In addition, an inadequate response or intolerance to at least two b/tsDMARDs with an appropriate wash-out period for the most recent used b/tsDMARDs was required. The use of oral prednisone at a stable daily dose of no more than 10 mg/day and/or a stable dose of csDMARDs were allowed. Major exclusion criteria included: uncontrolled other inflammatory diseases; history of unilateral or bilateral vagotomy; splenectomy; previously implanted electrically active medical devices; cancer within the past five years; an abdominal wall thickness > 2.5cm, or significant cardiovascular or surgical risk.

Investigational device

The Galvani system (Galvani Bioelectronics, Stevenage, UK) is a rechargeable neurostimulation system with a single lead connected to an Implantable Pulse Generator (IPG) designed to deliver electric stimulation to the splenic NVB (see Figure S1). The implantable system is designed specifically for laparoscopic implantation.

Procedures

Written informed consent was obtained from all participants before any study related procedure was performed. All inclusion and exclusion criteria were verified during visits with the rheumatologist and implanting surgeon. If all criteria were met, implantation of the device was performed laparoscopically under general anaesthesia (see supplementary Figure S2 for a schematic presentation of the implant). Following implantation and approximately 28 days recovery, chronic SpNS was initiated (Day 1). Stimulation amplitudes were gradually increased over a 28-day period (dose escalation) to their individual maximal tolerable dose (MTD) or a maximal amplitude of 20mA. Stimulation used a 2 ms pulse width and 10 Hz frequency (0.5s ON, 4.5s OFF). Six 5-minute therapy sessions were administered daily (at 2-hour intervals, during waking hours), automatically scheduled by the IPG. The parameters were derived from computational and translational studies [18–20]. Participants were able to have the stimulus amplitude increased up to visit Day 28 (Days 1, 4, 7, 14, and 28) if their maximal tolerable dose was not reached earlier. On Day 42 and 56, if remission was not achieved as defined by the DAS28-CRP > 2.6, the number of stimulation episodes could be increased up to 12 episodes a day during waking hours, and/or the stimulations could be divided over 24 hours (day and night). Device function was assessed during follow-up visits via review of IPG log files. The IPG is rechargeable and requires approximately 30 minutes of charging per week divided over approximately two sessions.

In Period 2, participants who continued to receive stimulation were assessed every month for the first 3 months, thereafter every 3 months for the first 2 years, and then every 6 months thereafter up to 5 years in Period 2. Participants with the system in hibernation mode (no stimulation) were not assessed for efficacy measurements, however they were followed up for safety every 6 months. In Period 2, the management of RA medication and stimulation parameters could be adjusted based on the level of disease activity and symptoms experienced by participants.

Endpoints and assessments

The primary outcome was the safety, feasibility, and tolerability of device implantation and chronic splenic neuromodulation, including the incidence of procedure- or device-related adverse events and unanticipated adverse device effects. The key secondary outcome was change in serum cytokines and the device performance as assessed by evaluating the Device Deficiencies (DD). The key exploratory outcomes included the change from Baseline (BL) in clinical disease and patient-reported outcomes at all assessment timepoints in Period 1 and 2. These includes Disease Activity Score 28-C-reactive protein (DAS28-CRP), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), Health Assessment Questionnaire Disability Index (HAQ-DI), and other patient-reported outcomes (pain, fatigue, and global assessment of disease). Other exploratory outcomes included biomarker analysis.

Safety

(Serious) Adverse events ((S)AEs), (Serious) Adverse Device Events ((S)ADEs), and Device Deficiencies (DDs) were collected throughout the study and coded using MedDRA (version 26.1). Adverse event severity and relationship to the study device was evaluated by site investigators, with independent oversight by the study Data Safety Monitoring Board (DSMB). Safety was also assessed through the evaluation of potential abnormalities in safety laboratory results, treatment-induced changes in 12-lead electrocardiogram (ECG) and blood pressure assessed during in-clinic visit.

Biomarkers

Serum cytokine and chemokine assays

For serum analysis, samples were processed in separator tubes, centrifuged at 1500 g for 15 min, and stored at -70°C . Cytokine and chemokine concentrations were measured using Meso Scale Discovery (MSD) S-PLEX and V-PLEX.

Flow cytometric analysis of surface markers, signalling, and transcription factors

Peripheral blood mononuclear cells (PBMCs) were isolated from EDTA-treated blood by density gradient centrifugation and cryopreserved in DMSO prior to flow cytometric analysis. For surface phenotyping, cells were thawed and stained with a viability dye and antibodies, including surface markers used to define Th17 ($\text{CD3}^{+}\text{CD4}^{+}\text{CXCR3}^{-}\text{CCR6}^{+}$) and TH1 ($\text{CD3}^{+}\text{CD4}^{+}\text{CXCR3}^{+}\text{CCR6}^{-}$) populations.

For phospho-flow and transcription factor analysis, PBMCs were stimulated using a cell stimulation cocktail including cytokines (IFN- α , IL-2, IL-6, IFN- γ and IL-4), PMA/ionomycin, LPS, and T cell activation beads (Miltenyi Biotec) at 37°C for 15 minutes, alongside unstimulated and fluorescence minus one control. Cells were stained for surface markers during the stimulation period. Following stimulation, cells were fixed and subsequently permeabilised prior to intracellular staining for pSTAT3. Data were acquired on an Attune NxT flow cytometry (Thermo Fisher Scientific) and analysed using FlowJo software.

Specialised pro-resolving mediators

Blood was collected in K2 EDTA tubes, inverted 10 times, then centrifuged at $2000 \times g$ for 20 min at room temperature. Plasma was collected into micro tubes and immediately snap-frozen by placing into a Coolrack M15 on dry ice for consistent freezing and stored at 70°C or lower before analysis. Lipid mediator analyses were conducted via LC-MS/MS-based profiling, as described previously [21].

Statistical analysis

No hypotheses were tested, and no sample size calculations have been performed. Demographics and patient characteristics, and safety data are summarised descriptively in tabular format. Efficacy and biomarker data are presented per individual in graphic format as appropriate with no formal statistical analyses performed. Individual outcomes were presented as changes over-time relative to Baseline (BL; Day 1, Period 1), unless otherwise noted. No formal statistical analysis was performed. Full statistical analysis is provided as a supplementary file (S2.)

RESULTS

Participants were implanted between November 2021 and November 2024. Database lock for data analysis was performed on October 31st, 2025. At this point, all participants had completed the primary reporting period triggered by the last participant's last visit in Period 1 and a minimal follow-up duration of 24 weeks in Period 2. Due to financial constraints the study was terminated prematurely on 24th of April 2026.

Demographic and clinical characteristics of the study subjects

Baseline clinical features of all five participants enrolled in the study are summarised in Table 1 with data presented as mean $\pm$ SD unless otherwise stated. Three (60%) participants were female, the median age was 63.2 ± 6.87 years, and the mean RA disease duration was 17.4 ± 15.85 years. One participant (3) with a well-documented history of seropositive RA at initial diagnosis, with peak values of 189 IU/mL for Rheumatoid Factor (RF) and 39 U/mL for anti-cyclic citrullinated peptide (anti-CCP), presented with equivocal RF (4.1 IU/mL) and negative anti-CCP (1.0 U/mL) at the time of screening. Per inclusion criteria, all participants had an inadequate response to at least two b/tsDMARDs before enrolment, with a mean of 6.0 ± 5.24 prior therapies. All participants had been treated with at least one bDMARD and 60% with an tsDMARD (i.e. Janus Kinase inhibitor). Three participants were taking a stable dose of csDMARDs (methotrexate (n = 2); hydroxychloroquine (n = 1)) as background medication at enrollment in the trial and minimally throughout Period 1. The mean DAS28-CRP was 4.6 ± 0.98 with a Swollen Joint Count (SJC) of 5.2 ± 3.83 and a Tender Joint Count (TJC) of 11.0 ± 6.93 , indicating patients had moderate to high RA disease activity at screening. At the time of enrolment three participants carried medical diagnoses that significantly impacted their health. Participant 2 was diagnosed with alopecia totalis in 1991, with epilepsy in 2017, and monoclonal gammopathy of unknown significance in 2019. Participant 3 had a pre-existing treatment refractory complex regional pain syndrome type 1 (CRPS-1) in the right arm diagnosed in 2010. Participant 5 had a history of cardiac arrhythmia (specifically Atrioventricular Nodal Reentrant Tachycardia (AVNRT) and Paroxysmal Atrial Fibrillation (PAF)), diagnosed in 1991 and treated with amiodarone. In 2018 they were diagnosed with unclassifiable fibrotic lung disease that was most likely related to rheumatoid arthritis.

Table 1
Baseline demographics and clinical characteristics of the study subjects in the splenic neuromodulation trial.

Characteristic	All (N = 5)
Age (years)	63.2 ± 6.87
Gender (Female)	3 (60%)
Race	
White	5 (100%)
BMI -Screening	23.7 ± 4.20
RA Duration since diagnosis (years)	17.4 ± 15.85
hsCRP, mg/mL	4.8 ± 4.44
Rheumatoid Factor (RF)	
Positive	4 (80%)
Equivocal	1 (20%)
Anti-cyclic citrullinated peptide (anti-CCP)	
Positive	4 (80%)
Negative	1 (20%)
Number of prior b/ts DMARDs	6.0 ± 5.24
Number of prior DMARDs:	1 (20%)
2	1 (20%)
3	3 (60%)
> 3	
DAS28-CRP	4.6 ± 0.98
CDAI	25.4 ± 13.48
SDAI	25.8 ± 13.90
TJC28	11.0 ± 6.93
SJC28	5.2 ± 3.83
HAQ-DI	1.1 ± 0.46 (5)
Continuous data displayed as mean ± SD (n); Categorical data displayed as n, the number of participants with that particular response, and percentages.	

Safety related to the device, study procedure and stimulation

Across all study periods, 31 AEs were reported among the five participants; of those AEs, 27 (87%) were unrelated to the study device and associated stimulation (Table 2). Four AEs were assessed as having a possible, probable, or causal relationship to the study device or stimulation: tingling in the face (Paraesthesia), abdominal discomfort, temporary increase in heart rhythm during night-time stimulations (Tachycardia), and device dislocation. The tingling in the face was reported in Period 1 on stimulation in one participant, was mild in intensity and did not require any action with stimulation. The abdominal discomfort

reported in Period 2 on stimulation in the same participant, was mild in intensity and resolved within 15 days without any action taken with the stimulation.

Two AEs were categorised as an Adverse Device Effect (ADE). The increase in heart rhythm was noted on a personal watch that provided physiological monitoring when being awoken by some of the night-time stimulations. However, this was not demonstrated during any clinical assessments using medical grade diagnostic equipment and resolved upon reducing the stimulation dose with 1 mA (from 16 to 15 mA). The second ADE, device dislocation, was described as device dislodgement during the implant procedure. The device was, as a precaution, replaced with a new device and the initial dislocation had no long-term impact on stability of the new device in the chronic phase.

Since the device dislocation occurred during surgery with a related AE, it was also categorized as a study procedure-related AE, and was described as bleeding caused by cuff dislodgement. The event was non-serious, resolved on the day of onset, and was managed intraoperatively with bipolar electrocautery and use of a haemostatic matrix. This event did not adversely affect the participant's post-operative recovery. Three other procedure-related AEs, post-operative swelling in one participant and post-operative pain in two participants, were mild and resolved in the post-operative period with one participant taking an opioid for 6 days post-surgery and over the counter pain medication when needed.

Overall, the adverse event profile was characterized predominantly by mild to moderate events, most of which resolved, and the majority were assessed as not related or unlikely related to the investigational device or stimulation.

Three SAEs were reported in two participants in Period 2; all unrelated to the intervention. The event in Participant 1 included a urinary tract infection when the device was in hibernation mode (Week 65 in Period 2), which needed hospitalisation and i.v. antibiotics. The second SAE in Participant 2 was appendicitis which occurred in Week 20 in Period 2 when the participant was on stimulation in combination with adalimumab. The device was placed in hibernation mode pending treatment of the appendicitis and one dose of adalimumab was omitted. The appendicitis resolved and the participant was awaiting an appendectomy at the time of database lock. The third SAE in the same Participant 2 was a fall resulting in a dislocation fracture of the shoulder which was treated conservatively without surgical intervention at the time of the database lock.

No fatal adverse events, serious adverse device effects (SADEs), or deaths were reported during the clinical investigation.

One device deficiency (DD) was reported in this clinical trial. The first participant (Participant 1) presented at the Week 12 visit (Day 84) with an appearance of intermittent increases in impedance over time, starting on Day 71, resulting in missed therapies which was noted in the system log files. Stimulation was permanently discontinued and the device was set to hibernation mode. The participant was followed in Period 2 for device implant safety only. This event was recorded as a DD and was not considered an ADE because it did not result in any harm to the participant. Root cause analysis revealed that the DD most likely involved a stimulation lead break close to the IPG. As a result of the DD, the stimulation lead design was refined to add a second strain relief tab. In all subsequent participants impedance values were within the pre-defined range during the entirety of their implantation period implying a fully functional device.

The longer-term safety assessment of the implant procedure and system as assessed by a computed tomography angiogram (CTA) taken approximately four-months post implant revealed in all participants that the system was still in place with no evidence of device migration. In addition, no intra-abdominal pathology caused by the surgical implant procedure, the system, or stimulation was observed.

Table 2
Adverse Events and Serious Adverse Events by Type and Relation to Study Device.

Characteristic	Total Events	Total Participants ¹
Any Adverse Events (AE/ADE)	31	5
Unrelated, Adverse Events (AEs) ²	27	5
Related, Adverse Events (AEs) ³	4	2
Study Device AEs ⁴	2	1
Discomfort	1	1
Paraesthesia	1	1
Adverse Device Effects (ADEs) ⁵	2	1
Device dislocation	1	1
Tachycardia	1	1
Study Procedure, Related AEs ³	4	3
Device dislocation	1	1
Post procedural swelling	1	1
Procedural pain	2	2
Unrelated, Serious Adverse Events (SAEs)	3	2
Serious Adverse Device Effects (SADEs)	0	0
Death	0	0
AEs Leading to Study Discontinuation	0	0
<i>All adverse events occurring during the surgery/recovery period and throughout follow-up periods are included in this table. Event types listed are based on MedDRA Version 26.1 preferred terms.</i> ¹Data presented as the number of participants with at least one event of that type. ²Unrelated AEs include the events categorised as not related or unlikely to be related to the device. ³Related AEs include the events categorised as possibly, probably, or causally related. Rheumatoid Arthritis and study procedure relatedness determined by investigator only. ⁴Includes adverse events categorised as possibly related to the device. ⁵Includes adverse events categorised as probably or causally related to the device.		

Treatment exposure

All participants received in-clinic dose escalation of stimulation intensity on all visits from Day 1 to Day 28 up to their individual MTD, ranging from 3 to 16 mA (Fig. 2, Table 3). At the end of each dose-escalation session, therapy was programmed for 5 minutes delivered six times a day (2-hour interval) during waking hours. If discomfort was experienced, the amplitude was reduced to a tolerable level. Overall, stimulation was well tolerated with sensation localised mostly internally in the upper left abdomen which did not result in any clinically significant change in vital signs including blood pressure and 12-lead ECG taken immediately after in-clinic stimulations. In addition, clinical biochemistry and haematological parameters did not indicate any clinically significant changes.

In Week 6 and 8 (Day 42 and Day 56), all five participants elected to modify their therapy paradigm since remission, as defined by the DAS28-CRP > 2.6, was not achieved. Four participants received stimulation equally divided over 24 hours instead of only during waking time and increased the number of stimulations over 24 hours to 12. Participant 5 increased the number of stimulations to 12 times daily. In this participant due to sensation the stimulation dose was reduced on Day 84. The

stimulation profile per participant in Period 1 is provided in Table 3. Due to the small number of participants, the effect on clinical disease activity with the change in dose ranging could not be evaluated, however stimulation 6 or 12 times a day, delivered over waking hours or the entire day, was well tolerated.

In Period 2, except for Participant 1 with the lead break, all four participants initially continued stimulation. During this period, two participants (2 and 5) had the device placed in hibernation mode; Participant 2 due to appendiceal abscess and Participant 5 due to the device system not meeting their personal expectations. At the time of database lock, the total exposure to active stimulation was approximately 3.4 years across all participants.

Table 3
Stimulation profile per participant in Period 1.

Pt	1			2			3			4			5		
Visit	mA	N	Day/ Night	mA	N	Day/ Night	mA	N	Day/ Night	mA	N	Day/Night	mA	N	Day/Night
D1	5	6	Day	5	6	Day	5	6	Day	2	6	Day	5	6	Day
D4	10	6	Day	7	6	Day	10	6	Day	2	6	Day	10	6	Day
D7	13	6	Day	9	6	Day	12	6	Day	2.5	6	Day	12.5	6	Day
D14	12	6	Day	10	6	Day	13	6	Day	2.5	6	Day	10	6	Day
D28	12	6	Day	11	6	Day	16	6	Day	3	6	Day	10	6	Day
D42	12	6	Day/ Night	9	6	Day	16	6	Day / Night	3	6	Day/ Night	10	6	Day
D56	12	12	Day/ Night	9	6	Day/ Night	16	12	Day / Night	3	12	Day/Night	10	12	Day
D70	NA	NA	NA	9	6	Day/ Night	16	12	Day / Night	3	12	Day/ Night	10	12	Day
D84	NA	NA	NA	9	12	Day/ Night	16	12	Day/ Night	3	12	Day/ Night	8	12	Day

mA: stimulation amplitude; **N:** Number of stimulations per 24 hours; **Day:** Stimulations over 12hr daytime period only (1–2 hr between sessions), **Day/Night:** Stimulation over 24hr period (2–4 hrs between sessions).

Efficacy

Change on disease-related outcome measures in Period 1 upon SpNS are shown in Fig. 3 as change from baseline, individual scores are shown in supplementary Figure S3. Participant 3 showed changes in DAS28-CRP compared to BL that exceeded the Minimal Clinical Important Difference (MCID) of ≥ 1.0 -point reduction [22] on all time-points assessed in Period 1, with a maximal decrease of -3.30 points at the Week 10 visit and reaching low disease activity (LDA) (Fig. 1A). For Participant 5 the MCID in DAS28-CRP reduction was reached in Week 4 and 6, being -1.63 and -1.40 respectively, though thereafter the reduction in DAS28-CRP was lost. The other three participants (1, 2, and 4) showed minimal or no change in DAS28-CRP after 12 weeks. The time courses for disease activity measures SDAI and CDAI (see supplementary Table S1), the SJC and TJC, and HAQ-DI (Fig. 3C-E) followed a similar pattern. Of particular note is that Participant 3 showed significant responses for HAQ-DI of -1.375, exceeding the MCID of 0.35 [22] and in the VAS arthritis pain score, with a near 100% reduction in pain at week 12.

In Period 2, Participant 3 continued stimulation monotherapy and the disease activity score and patient-reported outcome improvements were sustained across all parameters (Fig. 2 change from baseline, see for individual scores supplementary Figure S4), up to week 62 in Period 2. Remarkably, in parallel with improvement in this participant's RA symptoms, a treatment refractory CRPS-1, diagnosed in 2010, improved within days of stimulation and resolved completely one week after initiation of stimulation. Following the improvement in CRPS-1 symptoms, reduction of medication specifically taken for this condition was

managed and gradually reduced and/or stopped in Period 2 when the participant was demonstrating sustained symptom improvements. The gradual reduction in medication included the use of weak opioids, amitriptyline and pregabalin. All medication was fully stopped approximately 9 months (Period 2, Month 6) after start of treatment (see supplementary Table S2 for an overview).

For the other three participants completing 12 weeks of stimulation in Period 1, clinical disease outcome measures did not improve to a level exceeding the MCID. During Period 2 three participants started with adjunct therapy, stimulation in combination with a b or tsDMARD (Fig. 4 and supplementary Table S3). In week 38, approximately 12 weeks after start of adjunct therapy, Participant 4 demonstrated a reduction in DAS28-CRP compared to BL of -2.39 points, which was sustained after 24 weeks (Week 50) of adjunct therapy (-2.34 points reduction, final data point before database lock) (Fig. 4). In Participant 2 the device was placed in hibernation (stimulation OFF) 8 weeks after the start of adjunct therapy due to the appendicitis described in the safety section. At the time of database lock the participant was awaiting an appendectomy. Participant 5 started on high dose oral prednisone (see supplementary Table S3) at the start of Period 2, followed by adjunct therapy in week 20 of period 2. However, four weeks later in week 24 the participant elected to put the device in hibernation mode due to the device system not meeting their personal expectations.

Biomarkers

To assess changes in circulating immune markers following implantation, we first analysed plasma biomarkers at pre-implantation (Day 1) and week 12 (Day 84) using the MSD platform. The highest responder Participant 3 showed a distinct inflammatory biomarker profile over time compared to the non-responders, characterised by reduced pro-inflammatory cytokine levels including IL-17A, IL-6 and IL-1 β . Participant 1 was excluded from analysis due to the DD detected at Day 71 in Period 1 resulting in missed therapies. The heatmap (Fig. 5A) shows changes in plasma biomarkers between Day 1 and Day 84, presented as relative changes from pre-implantation levels. When examining individual cytokines, IL-17A showed the most pronounced decrease in the responder, whereas IL-17A increased across all non-responders over the same period (Fig. 5B). In contrast, IFN- γ showed a greater increase in the responder compared to non-responders at week 12.

To further explore cellular changes following implantation, we analysed peripheral Th17 (CD3⁺CD4⁺CXCR3⁻CCR6⁺) and Th1 (CD3⁺CD4⁺CXCR3⁺CCR6⁻) cell frequencies across Day 1, Day 28 and Day 84 in relation to IL-17A and IFN- γ responses observed in plasma (Fig. 6A–B).

The responder showed higher frequencies of both Th17 and Th1 cells at baseline compared to the non-responders. Th17 frequencies showed limited changes over time across all patients, including in the responder (Fig. 6A). In contrast, Th1 cell frequencies increased in the responder at Day 84, while non-responders displayed variable patterns (Fig. 6B).

We next assessed downstream signalling in Th17 cells by measuring STAT3 phosphorylation following stimulation. In several non-responders, responses to stimulation were limited or absent. Change in mean fluorescence intensity (Δ MFI) analysis (stimulated minus unstimulated) showed a clear reduction in STAT3 phosphorylation in the responder compared to the non-responders (Fig. 6C and D).

Finally, an assessment of specialised pro-resolving mediators was undertaken at 4hrs following stimulation on Day 1, Week 1 (Day 7), Week 4 (Day 28) and Week 12 (Day 84), compared to baseline pre-stimulation levels on Day 1. The responder Participant 3 displayed a differing profile compared to the non-responders. There was a trend for increased levels of D-series Resolvins (RvDs) up to Day 28 compared to baseline in the responder, that was primarily driven by an increase in RvD2 levels, whereas lower or decreased levels were evident in non-responders (Fig. 7). Example chromatograms for each Lipid mediator identified in samples derived in the clinical trial are shown in supplementary Figure S5.

DISCUSSION

This first-in-human, open-label, single-arm study demonstrated the preliminary feasibility, safety and tolerability of implantation of an active neuromodulation device to stimulate the splenic nerve in patients with D2T RA. No unexpected or unmanageable

device-, procedure-, or stimulation-related safety concerns were identified. AEs were generally mild, transient, or unrelated to implantation or stimulation. CTA imaging approximately four months after implant confirmed that the system remained stable, with no pathologies linked to the procedure, device, or therapy. In the highest responder Participant 3, consistent improvement was seen across multiple disease activity and patient-reported outcome measures, supported by exploratory biochemical endpoints showing trends consistent with modulation of inflammatory pathways. These preliminary findings support further investigation of SpNS as a novel treatment approach in this population.

Chronic SpNS was safe and feasible across a range of stimulation amplitudes with participants' individual MTD ranging between 3 and 16mA. Up to Week 6 (Day 42), stimulation was delivered as six 5-minute sessions spaced every two hours during waking hours. In four participants, this regimen was expanded to twelve sessions evenly distributed every two hours over a 24-hour period; one participant received 12 stimulation every hour during day-time only. Both dosing schedules were well tolerated, and any sensation was mild in nature and night-time stimulation was not reported to interfere with sleep.

Clinical responses upon treatment with SpNS only were heterogeneous, a finding expected in a D2T population that has failed multiple therapies with different modes of action. In Period 1, two participants (3 and 5) demonstrated reductions in DAS28-CRP that exceeded the MCID at one or more time points. Participant 5 lost the effect after 8 weeks.

The highest responder, Participant 3, had failed on three previous bDMARDs. This participant had undergone seroconversion to equivocal/seronegative status prior to enrolment despite previously high autoantibody titres. Autoantibody levels in RA can fluctuate substantially over time due to prior treatments [23], natural variation in autoreactive B-cell activity [24], or changes in the inflammatory microenvironment, even in patients with ongoing moderate-to-high disease activity [25]. Following the onset of stimulation, the decrease in DAS28-CRP exceeded the MCID at all assessed time points and reached low disease activity by Week 10. Improvements were also observed across additional composite disease activity scores, physical function, and pain measures. In this participant a reduction of > 80% in the VAS arthritis pain score was observed from Week 12 onwards. These clinical benefits were sustained throughout continued stimulation in Period 2, with ongoing SpNS monotherapy for 62 weeks. Even when achieving targeted remission of joint inflammation, persistent pain remains a primary clinical problem in RA [26]. Existing pharmacological analgesics frequently lack sufficient long-term efficacy and are accompanied by adverse side effects [27]. Notably, this participant also achieved sustained drug-free remission of the long-standing treatment refractory CRPS-1. CRPS-1 is characterized by neuroinflammation, autonomic dysregulation and elevated pro-inflammatory cytokines [28, 29], to some extent similar to RA. Since inflammatory cytokines play an important role in CRPS-1 development, treatments frequently target this pathway. Anti-inflammatory therapies, ranging from oral glucocorticoids to targeted biologic drugs like anti-TNF- α agents, have been successfully used to reduce clinical severity and promote recovery [27]. Although these treatments show an effect particularly when administered early in the disease, it can be envisioned that chronic SpNS, which modulates the inflammatory response including a reduction in pro-inflammatory cytokines, reduces the pathology of CRPS-1.

Together these results imply that SpNS, in addition to reducing the disease activity scores, may have an important positive effect on pain. The improvement in both conditions suggests that SpNS may have broader neuromodulatory effects on shared neuro-immune pathways [29]. Of note, for this participant the stimulation amplitude was highest (16 mA), which may indicate a correlation between stimulation intensity and clinical response. Although these findings were observed in only one participant, they generate a mechanistic hypothesis that warrants further investigation in larger, controlled trials.

In contrast, the remaining four participants showed limited or no meaningful clinical improvement after 12 weeks of SpNS monotherapy in Period 1. In Participant 1, during IPG checks in Week 12 (Day 84), high impedance values were noted in the IPG log starting on Day 71 which resulted in intermittent therapy from this point. The device was placed in hibernation mode, and the participant was excluded from efficacy analysis after the Day 56 visit. Of the three participants changing to adjunct therapy, some clinical improvements were observed. Participant 4 started on the combination of filgotinib and stimulation and exhibited clinically meaningful reductions in disease activity with a DAS28-CRP close to remission in week 38 and 50 of Period 2. Interestingly, this participant was treated with filgotinib for 12 months before participating in the trial and had then stopped taking this medication due to lack of efficacy. Participant 2 demonstrated an initial response to adjunct treatment, adalimumab and stimulation. However, after week 20 in Period 2 the CRP level was increasing contributing to an increase in DAS28-CRP

level. At this point the participant was diagnosed with appendicitis, and the stimulation was turned OFF and the participant was excluded from further efficacy analysis. At the start of Period 2, Participant 5 received high-dose prednisone (Table S3) in combination with stimulation resulting in a significant decrease in DAS28-CRP likely due to the prednisone treatment. In week 20 (Month 1 in Period 2) adjunct therapy, abatacept and stimulation, was started. However, the participant discontinued SpNS in week 24 after start of stimulation due to personal unmet expectations of the therapy. Due to the short duration of the adjunct therapy and the effect of the high dose prednisone treatment in the week before, the efficacy of the adjunct therapy could not be evaluated in this participant.

In RA, Th17 cells and IL-17A drive synovial inflammation, cartilage degradation, and bone erosions through STAT3/ROR γ t signalling [31–33]. The highest responder, Participant 3, exhibited a unique cytokine profile after 12 weeks of SpNS, characterised by reduced pro-inflammatory cytokines, especially IL-17A and an increase in IFN- γ . These cytokine shifts were not seen in the non-responders. In parallel, the responder displayed higher baseline frequencies of both Th17 and Th1 cells compared with non-responders, followed by a selective increase in Th1 frequency and a pronounced reduction in stimulated STAT3 phosphorylation within Th17 cells at week 12. These findings are consistent with preclinical evidence that electrical stimulation of the splenic nerve modulates immune cell function via adrenergic receptors, ultimately suppressing pro-inflammatory cytokine production [15–17]. Although it is well established that high levels of IFN- γ can inhibit the differentiation of function of pathogenic Th17, it cannot be excluded that an intercurrent tooth infection developed around Week 8 (Day56) in Period 1, and was treated with a 7-day course of amoxicillin, may have contributed to the elevated IFN- γ level observed at Week 12 (Day84). Symptoms of the infection had subsided one week prior to the Week 12 assessment. Interestingly, while Th17 cell frequencies remained stable and were in fact higher in the responder at baseline, downstream STAT3 phosphorylation decreased over time. This suggests that despite the phenotypic presence of Th17 cells, their functional activity may have been reduced, potentially contributing to the lower IL-17A levels observed following stimulation. Although IL-17/Th17-driven inflammation is typically more prominent in early RA than in long-standing disease [34], this participant may represent an IL-17 defined pathotype despite long-standing D2T RA [35].

In addition, elevated levels of RvDs were observed in the responder (Participant 3) compared to non-responders, with specifically an early onset through to Day 28. RvDs are specialized pro-resolving lipid mediators, derived from omega-3 fatty acids, that actively attenuate inflammation, promote tissue repair, and restore immune homeostasis, thereby counteracting chronic inflammation [36]. This observed increase in RvDs, and early onset, is consistent with our previous preclinical findings in a chronic porcine model of splenic stimulation [17].

Clinical studies of cervical vagus nerve stimulation in RA have shown that neuromodulation can attenuate inflammatory activity and reduce disease activity [6–8]. Since the vagus nerve innervates multiple organs, off-target effects limit the maximal tolerable dose for cervical vagus nerve stimulation and likely also limit the therapeutic dose accessible for this indirect therapy [11]. In contrast, SpNS targets the splenic nerve which is the downstream organ-specific nerve that selectively exerts the immune modulatory effects on the circulating immune cells present in the spleen without being limited by the off-target side effects in other organs inherent to cervical vagus nerve stimulation. This selective near organ stimulation is intended to allow a higher tolerable stimulation dose contributing to a greater reduction in disease activity and more patients responding to neuromodulation therapy.

A prior feasibility study in patients undergoing minimal invasive esophagectomy demonstrated that implantation, intraoperative stimulation, and removal of the neuromodulation device during a single surgical procedure was safe and associated with reductions in postoperative inflammatory markers [19]. The current findings extend these observations by showing that chronic implantation and repeated stimulation over months to years is feasible, has an acceptable safety profile, and is well tolerated in patients with chronic inflammatory disease.

This pilot study has limitations typical of an early feasibility trial. The study was not powered for statistical hypothesis testing and the small sample size limits firm conclusions regarding efficacy and biomarker responses. In partially subjective conditions such as RA and chronic pain, placebo effects and regression to the mean may influence patient-reported outcomes. In addition, while the stimulation amplitude was titrated to the participant's MTD, this feasibility study was not statistically

powered to perform an evaluation of the stimulation dose impact on overall change in disease activity and potential therapeutic efficacy. Optimization of other components of the stimulation parameters was not investigated in relation to the MTD of an individual participant or in relation to the potential efficacy. Thirdly, the follow-up duration in Period 2 ranged, at the time of data cut, from 24 weeks to 62 weeks limiting conclusions regarding long-term efficacy, safety, and device performance, which is important for treating a life-long chronic disease such as RA. Additionally, the heterogeneity of the D2T RA population introduces variability that makes it challenging to identify predictors of response or to generalise findings broadly.

CONCLUSION

In summary, this pilot study demonstrated a favorable safety profile, and technical feasibility of both the implant procedure and chronic SpNS with an investigational active implantable neuromodulation device. The SpNS was well tolerated and preliminary signals of a clinical effect and biomarker responses were observed. Although the small sample size limits conclusions regarding effects of adjunct therapy, these findings suggest that SpNS may confer benefit either as monotherapy in selected individuals or as an adjunct to pharmacological treatment in others. These results support further evaluation in randomised, sham-controlled trials to evaluate levels of efficacy, optimise stimulation parameters and further delineate the mechanisms and clinical indications for SpNS.

Abbreviations

ADE	Adverse device event
AE	Adverse event
AVNRT	Atrioventricular Nodal Reentry Tachycardia
b/ts	Biological or targeted synthetic
BL	Baseline
CCP	Cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
CRP	C-Reactive peptide
CRPS-1	Complex regional pain syndrome type 1
cs	Conventional synthetic
CTA	Computed tomography angiogram
D2T	Difficult to treat
DAS28-CRP	Disease Activity Score 28 for Rheumatoid Arthritis with CRP
DD	Device deficiencies
DMARD	Disease-modifying anti-rheumatic drugs
ECG	Electrocardiogram
HAQ-DI	Health Assessment Questionnaire Disability Index
IPG	Implantable pulse generator
LDA	Low disease activity
LTFU	Long-term follow up
MCID	Minimum clinically important difference
MIE	Minimal invasive esophagectomy
MTD	Maximum tolerated dose
NA	Noradrenaline
NVB	Neurovascular bundle
PAF	Paroxysmal Atrial Fibrillation
PBMC	Peripheral blood mononuclear cell
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RvDs	D-series resolvins
SADE	Serious adverse device event
SAE	Serious adverse event
SDAI	Simplified Disease Activity Index
SJC	Swollen joint count
SpNS	Splenic nerve stimulation

TJC	Tender joint count
VNS	Vagus nerve stimulation

Declarations

Ethics approval and consent to participate

The study followed the Declaration of Helsinki, ISO 14155:2020 Good Clinical Practice, and the EU Medical Device Regulation (Council Regulation 2017/745 concerning medical devices). The study was approved by the Medical Research Ethics Committee Amsterdam UMC (MREC, Amsterdam UMC) and the South East Scotland Research Ethics Committee 02 (SESREC02) under reference number NL84443.000.23/NL-007112 on the 17th of November 2023 and IRAS293980/21-SS-0009 on the 8th of March 2021, respectively. All participants provided written informed consent before the data collection began.

Consent for publication

All subjects provided written informed consent for the publication of anonymized data.

Availability of data and materials

The datasets generated and analysed during this study are not publicly available. Galvani Bioelectronics is committed to enabling qualified external researchers to request access to anonymised patient-level data and supporting clinical documents from eligible studies. Data-sharing requests are evaluated and approved based on scientific merit and feasibility. All shared data are anonymised in accordance with applicable laws and regulations to protect participant privacy. For further information on the process, or to submit a request, please contact Galvani Bioelectronics.

Competing interests

Authors C.B. and O.R. are employees of GSK; Authors K.F., E.I., P.H.M., D.C., H.A., A.W., D.M.S., I.G., R.A., and M.J.V are employees of Galvani Bioelectronics/GSK; Authors N.B., N.B.J., M.D.P.L., C.S.G. and S.W.T. received consultancy fees and/or an institutional grant from Galvani bioelectronics; Authors J.C., M.R., O.D., J.D., M.S., A.V.T. and F.A.K., have no conflicts of interest to declare; Galvani Bioelectronics is owning patents related to the work presented in the publication.

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The sponsor of this study was Galvani Bioelectronics. The funding sources had a role in study design, data collection, analysis, and interpretation, and writing of this report.

Authors' contributions

All authors reviewed each draft critically for intellectual content; and approved the final version to be published. C.B., K.F., E.I., P.H.M., O.R., D.M.S., I.G., R.M.A. and M.J.V. conceptualised the study, designed the methodology, analysed and interpreted the data, and wrote the original draft of the paper. J.C., S.W.T, and F.A.K. performed the investigation and acquired the data, interpreted the data, and wrote the original draft of the paper. A.T.V., C.S.G, O.D., J.D. and P.H.M., performed the biomarker analysis and interpretation of data, and contributed to writing the paper. M.R., N.B., N.B.J, M.D.P.L, D.C., H.A., A.W., D.M.S., and I.G. performed the investigation, acquired the data, and evaluated the interpretation of the data.

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Figures

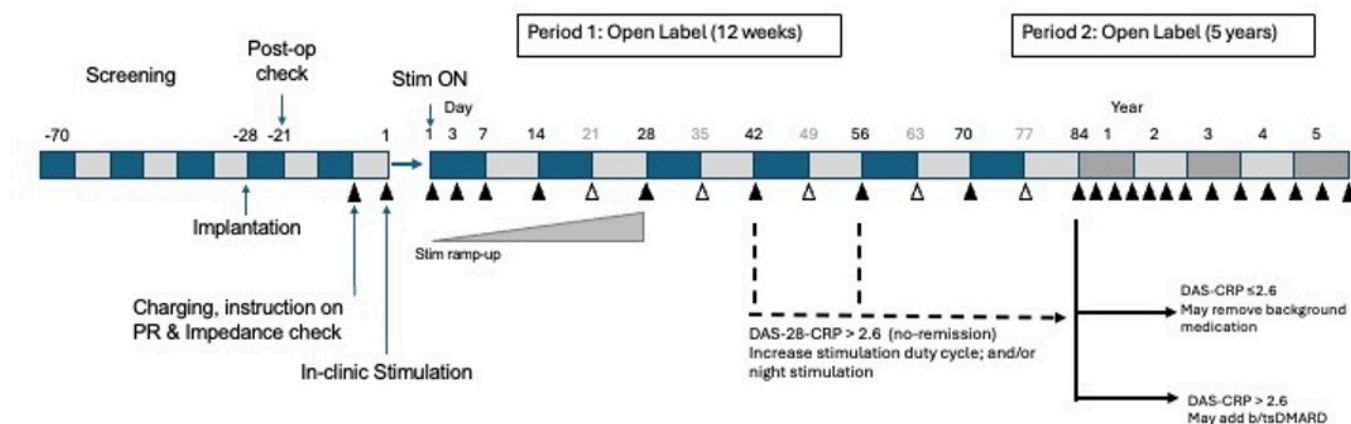


Figure 1. Study timeline. Schematic representation of the screening phase, implant, and planned visits during Period 1 and 2. ▲ in-clinic visits, △ phone calls.

Figure 1

See image above for figure legend.

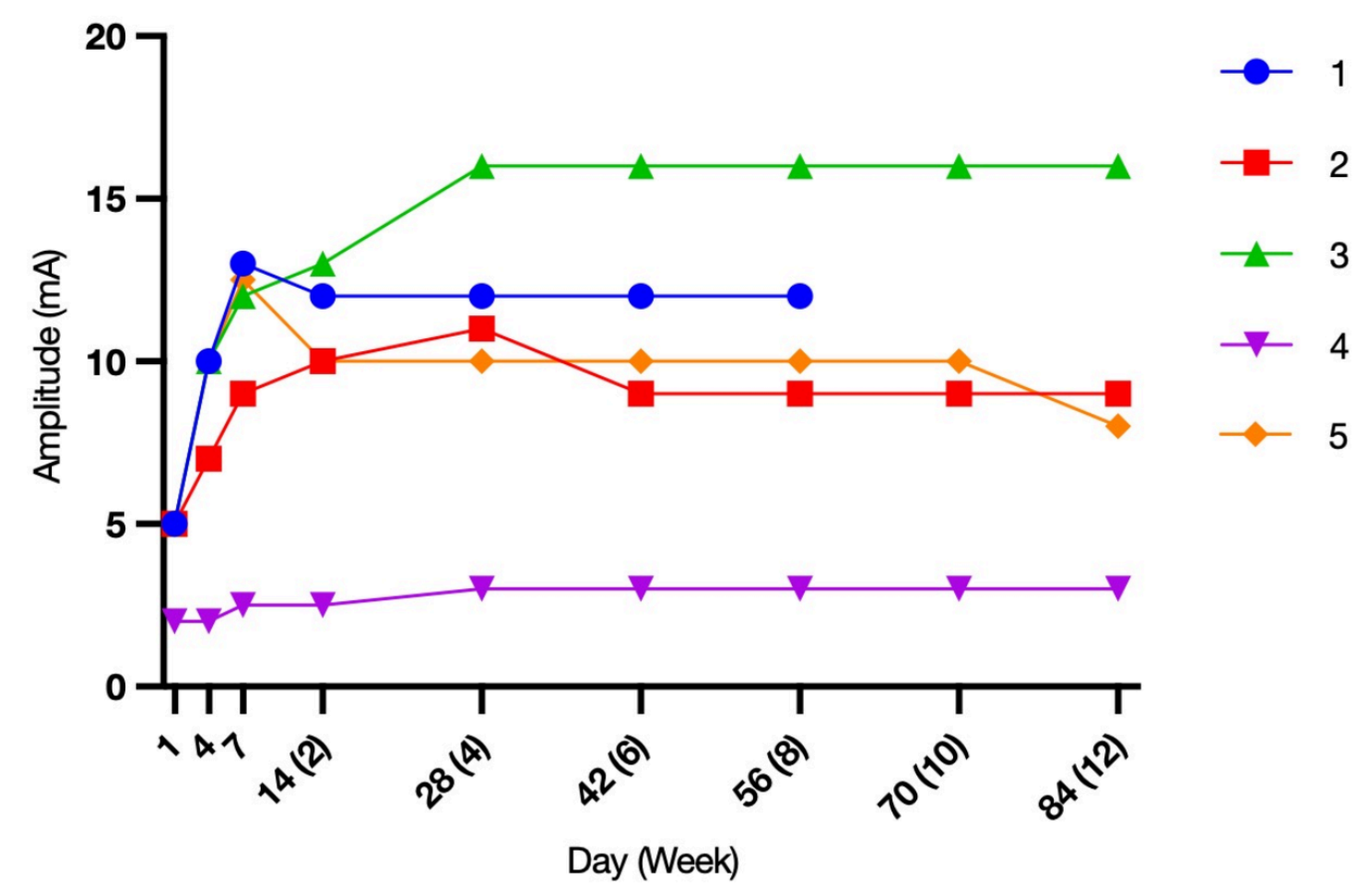


Figure 2

Stimulation dose-escalation over time in Period 1. The graph shows the stimulation intensity achieved at the end of each day of ramp-up, between Day 1 and Day 28 (Week 4) and the amplitudes up to Day 84. Participants were ramped-up to their individual maximum tolerated dose (MTD) that produced minimal to mild sensation. When the participant experienced moderate or severe discomfort, the amplitude was reduced to a tolerable level.

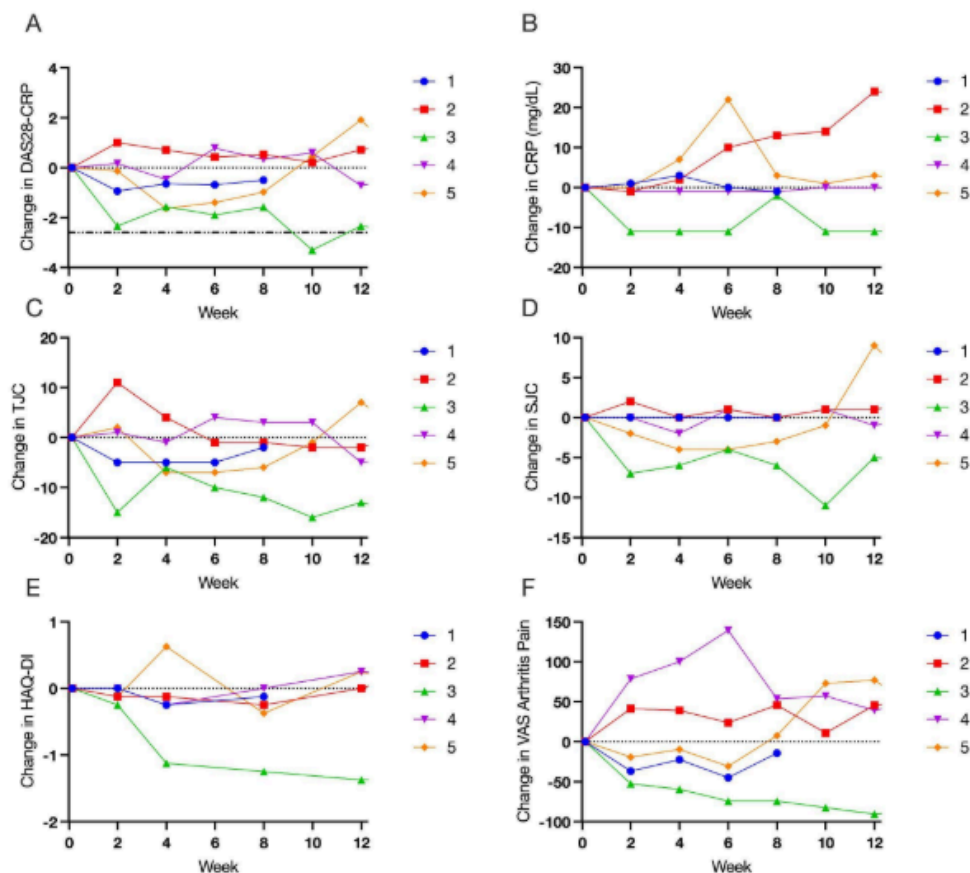


Figure 3

Disease Activity Scores and Patient-Reported Outcomes Over 12 Weeks of Treatment with Chronic Splenic Neuromodulation. All values are represented as the within-patient numerical change from Baseline (~28 days post-implant, immediately prior to initiation of chronic therapy on Day 1). (A) DAS28 - Disease Activity Score in 28 Joints; (B) CRP - C-Reactive Protein; (C) TJC - Tender Joint Count; (D) SJC - Swollen Joint Count; (E) HAQ-DI - Health Assessment Questionnaire-Disability Index; and (F) VAS Arthritis Pain - Patient's Assessment of Arthritis Pain Visual Analogue Scale (0-100). In all graphs, no change is indicated by a horizontal line (.....) at 0. In (A) horizontal dashed line (.....) indicates a change in DAS-28CRP of -2.6 (remission).

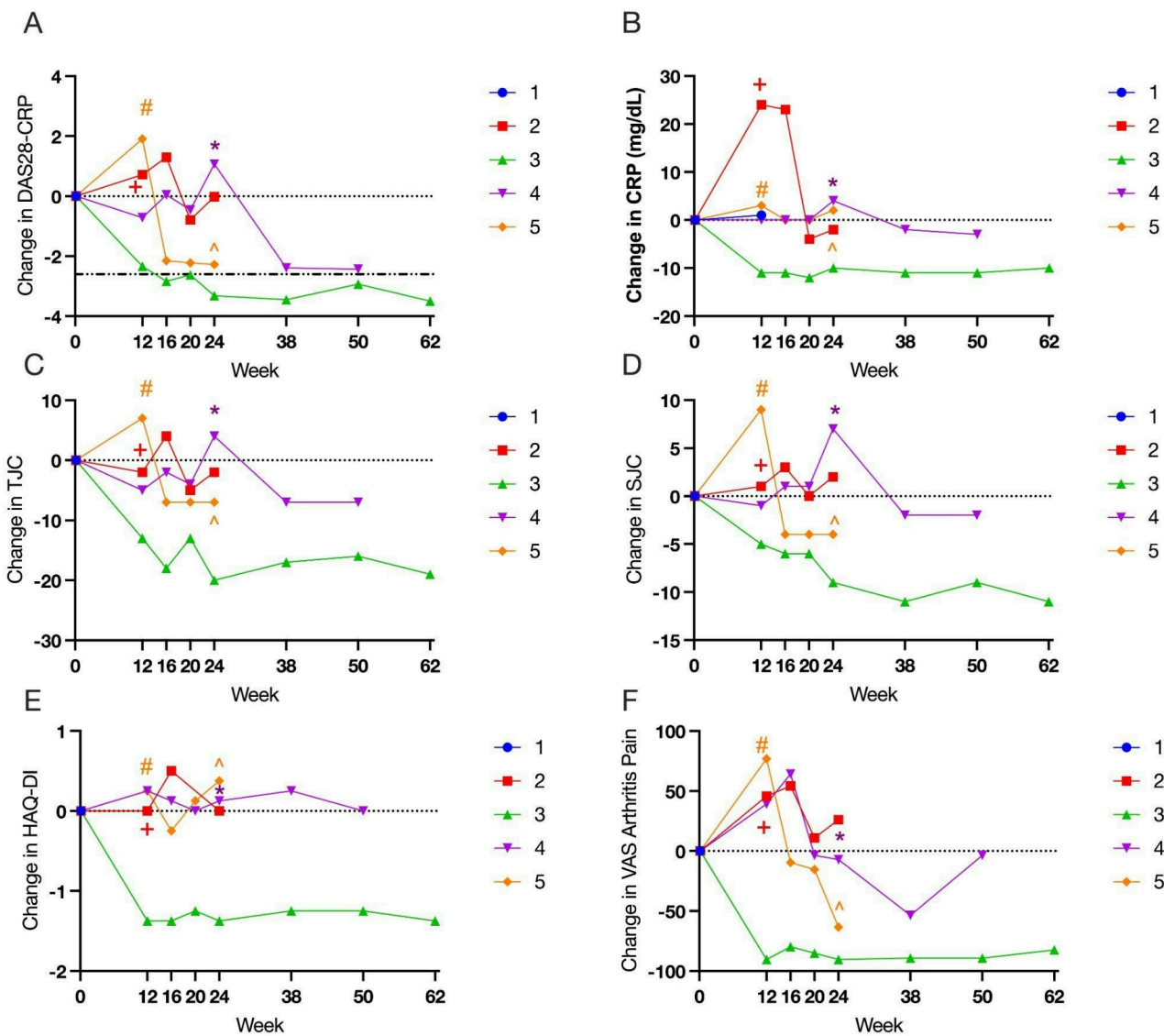


Figure 4

Disease Activity Scores and Patient Reported Outcomes at baseline and in Period 2 of Treatment with Chronic Splenic Neuromodulation. All values are represented as the within-patient numerical change from Baseline (~28 days post-implant, immediately prior to initiation of chronic therapy on Day 1). (A) DAS28 - Disease Activity Score in 28 Joints; (B) CRP - C-Reactive Protein; (C) TJC – Tender Joint Count; (D) SJC – Swollen Joint Count; (E) HAQ-DI - Health Assessment Questionnaire-Disability Index; and (F) VAS Arthritis Pain – Patient’s Assessment of Arthritis Pain Visual Analogue Scale (0-100). For Participant 2, + indicates the start of treatment with Amgevita (40 mg, s.c.). For Participant 4, * indicates the start of treatment with Filgotinib (200 mg, p.o.). For Participant 5, # indicates start of treatment with prednisone (20 mg, p.o., tapered to 10 mg by week 22) and ^ indicates start of treatment with Abatacept (500 mg, i.v.). In all graphs, no change is indicated by a horizontal line (.....) at 0. In (A) horizontal dashed line (.....) indicates a change in DAS-28CRP of -2.6 (remission).

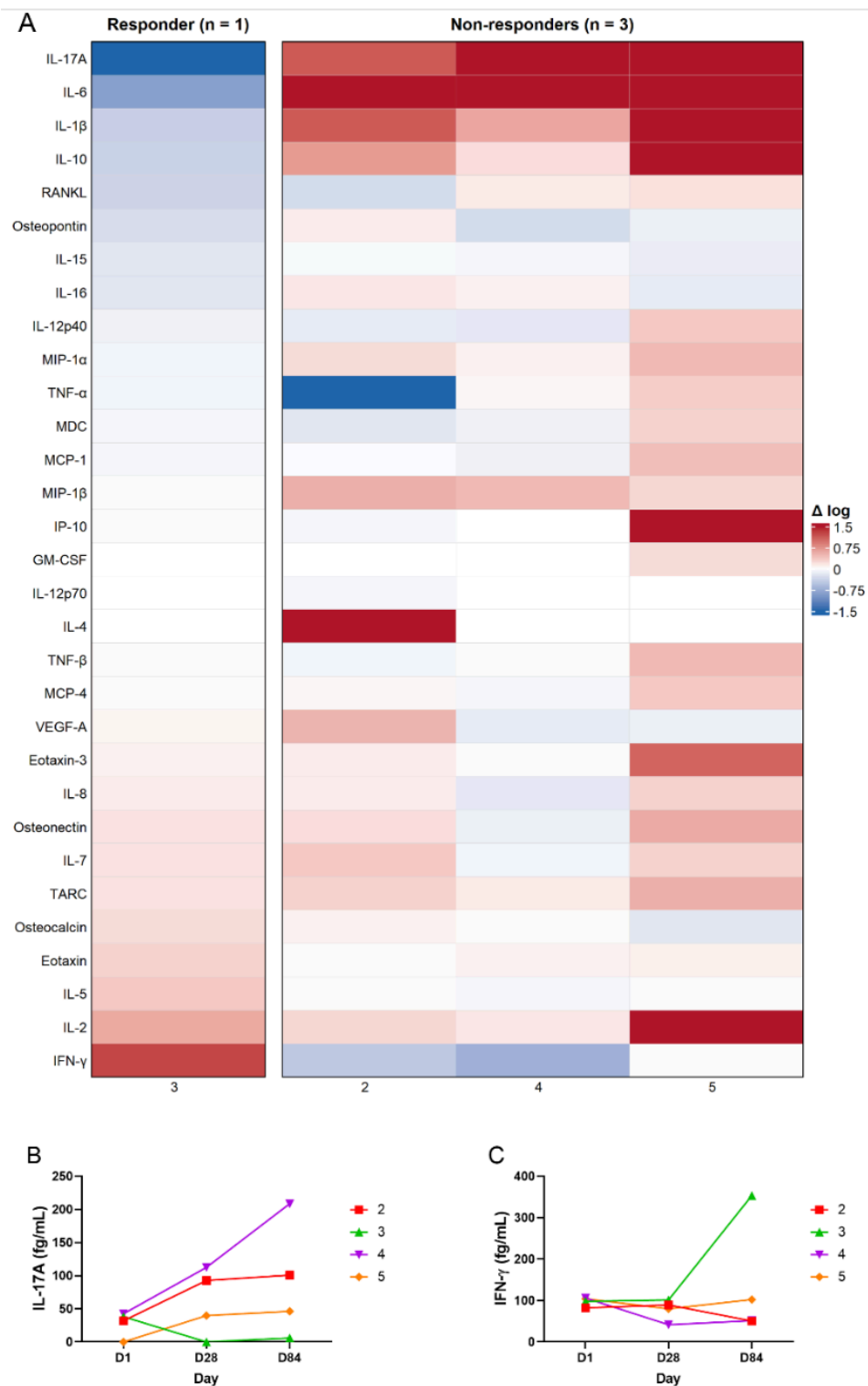


Figure 5

Changes in inflammatory plasma biomarkers over time in responder and non-responders. (A) Heatmap showing changes in plasma biomarkers between Day 1 and Day 84 after implantation. Values represent $\Delta \log$, calculated as $\log_{10}(\text{Day 84})$ minus $\log_{10}(\text{Day 1})$ for each participant. Biomarkers are ordered based on the magnitude of change in the responder, from lowest to highest. (B–C) Longitudinal changes in serum IL-17A (B) and IFN-γ (C) levels across Day 1, Day 28 and Day 84 for each patient.

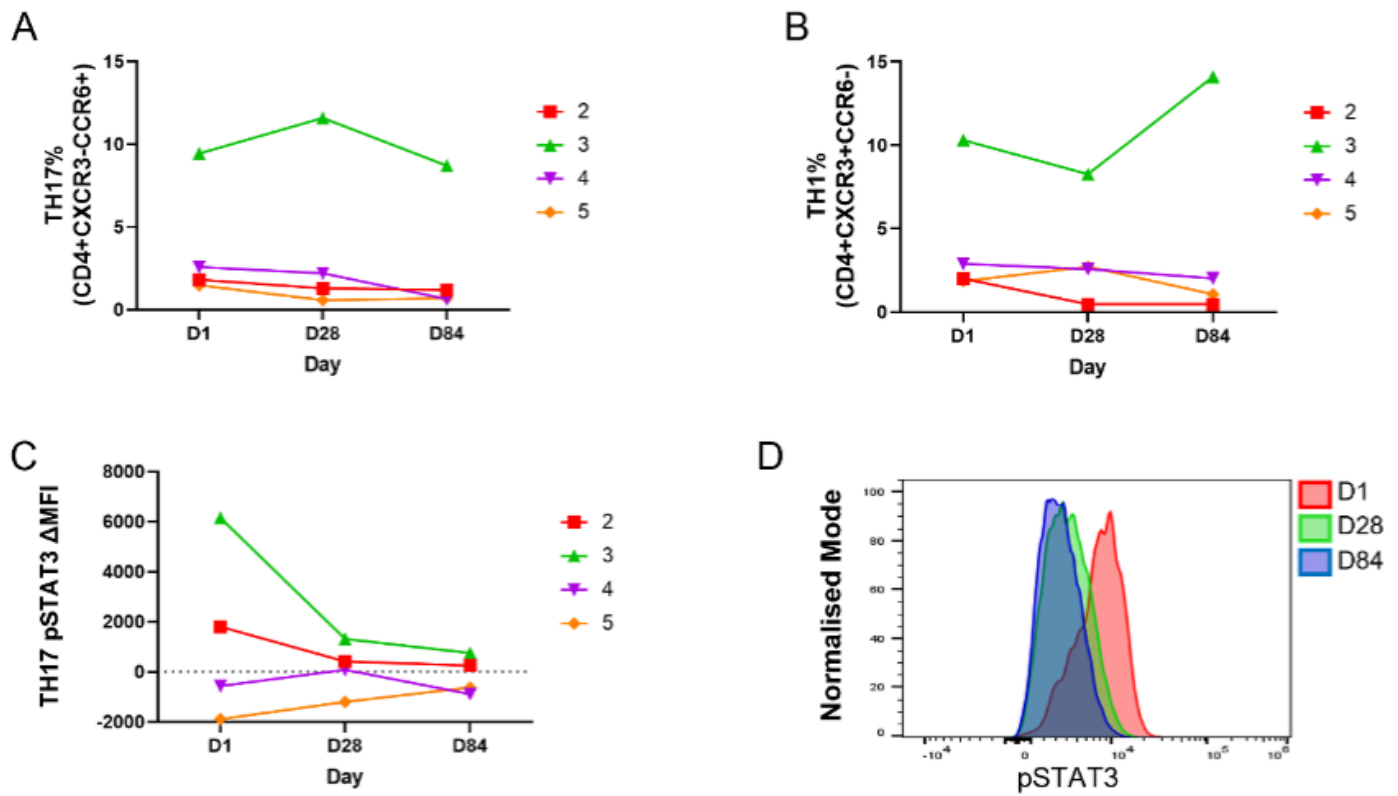


Figure 6

Longitudinal analysis of Th17 and Th1-associated cell markers and signalling pathways following implantation. (A–B) Frequencies of Th17 (CD4+CXCR3-CCR6+) (A) and Th1 (CD4+CXCR3+CCR6-) (B) cells across Day 1, Day 28 and Day 84 for each patient. (C) ΔMFI of pSTAT3 in Th17 cells, calculated as stimulated minus unstimulated conditions. (D) Representative histogram overlay showing pSTAT3 expression across timepoints specifically for the responder (Participant 3).

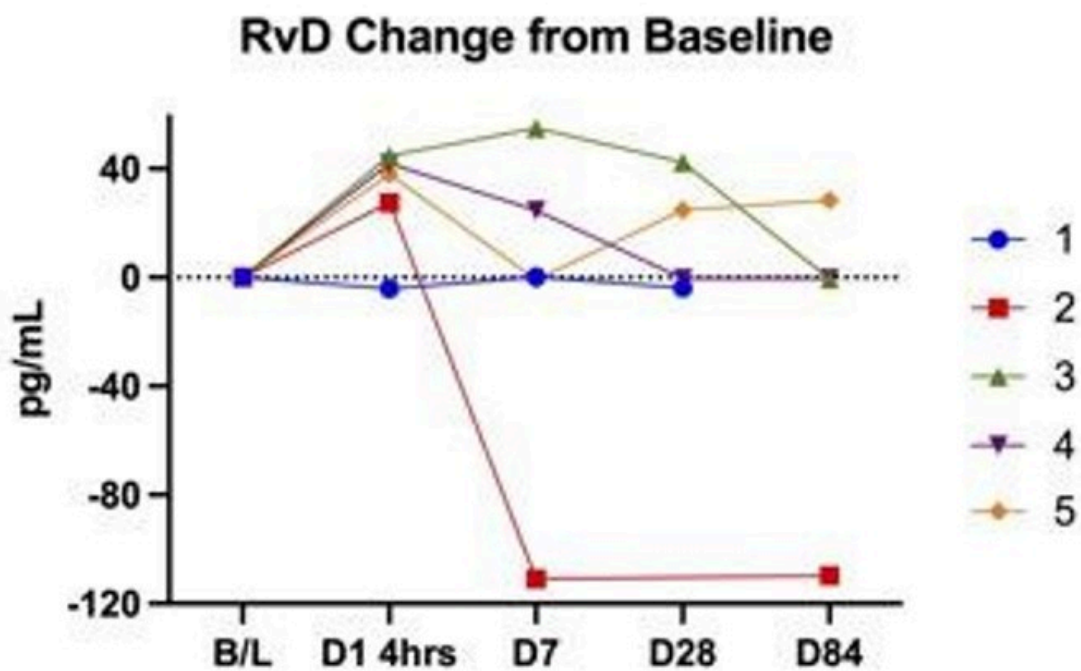


Figure 7

Change from baseline in plasma D-Series Resolvins over time in responder (n=1, Participant 3) and non-responders (n=4*). Plot shows the level of change over time from prestimulation baseline levels of RvDs (sum of RvD1, RvD2, RvD3, RvD4, RvD5, RvD5, 17R-RvD1, and 17R-RvD3) on Day 1 (4hrs following stimulation), Day 7, Day 28 and Day 84 for each participant. *Day 84 analysis for Participant 1 is missing due to DD noticed on Day 71.

Supplementary Files

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