



**A SINGLE ARM PILOT STUDY TO EVALUATE THE SAFETY AND FEASIBILITY
OF SPLENIC NERVE STIMULATION IN PATIENTS WITH RHEUMATOID
ARTHRITIS USING AN ACTIVE IMPLANTABLE DEVICE**

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ABBREVIATIONS

ACR	American College of Rheumatology
ADE	Adverse Device Effect
AE	Adverse Event
ANS	Autonomic Nervous System
AWT	Abdominal Wall Thickness
bDMARDs	Biological Disease Modifying Anti-inflammatory Drugs
BLE	Bluetooth® Low Energy
BMI	Body Mass Index
CDAI	Clinical Disease Activity Index
CP	Clinician Programmer
CRP	C-reactive protein
CT	Computed Tomography
DAS28-CRP	28 Joint Disease Activity Score-CRP
DD	Device Deficiencies
DMARDs	Disease Modifying Anti-inflammatory Drugs
DREs	Disease Related Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
e-CRF	electronic Case Reporting Form
EULAR	European League Against Rheumatism
EW	Early withdrawal
FCE	Field Clinical Engineer
HAQ DI	Health Assessment Questionnaire Disability Index
HR	Heart Rate
IB	Investigator's Brochure
IC	Informed Consent
ICF	Informed Consent Form
IFU	Instructions for Use
ID	Identity Document
IL-6	Interleukin-6
IR	Inadequate Response
IPG	Implantable Pulse Generator
ISO	International Organisation for Standardisation
JAKI	Janus Kinase Inhibitors
LPS	Lipopolysaccharide
LTFU	Long-Term Follow-Up
mA	milli Ampère
MCS	Mental Component Score
MHRA	Medicines & Healthcare products Regulatory Agency
MSBP	Mean Systolic Blood Pressure
MTD	Maximum Tolerable Dose
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NA	Noradrenaline
NVB	Neurovascular bundle
PCS	Physical Component Score
PI	Principal Investigator
PR	Patient Remote
PROs	Patient Reported Outcomes

RA	Rheumatoid Arthritis
RAID	Rheumatoid Arthritis Impact of Disease Questionnaire
REC	Research Ethics Committee
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SDAI	Simple Disease Activity Index
SF-36	Short Form survey
SPM	Specialised Pro-Resolving Mediators
SpNS	Splenic Nerve Stimulation
TNF α	Tumor Necrosis Factor Alpha
tsDMARDs	Targeted Synthetic Disease Modifying Anti-inflammatory Drugs
VAS	Visual Analog Scale
VNS	Vagus Nerve Stimulation
WOCBP	Woman of Childbearing Potential
WONCBP	Woman of Non Childbearing Potential

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with the Declaration of Helsinki, the International Organisation for Standardisation (ISO) standard on Good Clinical Practice (ISO 14155 (2011)), and the EU Medical Device Regulation (Council Regulation 2017/745 concerning medical devices). The essential requirements for the Galvani system will be assessed according to the EU Medical Device Regulation (EU) 2017/745.

1. PROTOCOL SYNOPSIS FOR STUDY GAL1039

Title:	A Single Arm Pilot Study to Evaluate the Safety and Feasibility of Splenic Nerve Stimulation in Patients with Rheumatoid Arthritis using an Active Implantable Device.
Study Design:	The study will be an open-label single arm study evaluating the safety and feasibility of stimulating the splenic neurovascular bundle (NVB) with an active implantable medical device. Five participants with active rheumatoid arthritis (RA) will be implanted with a device and following a recovery period of at least 28 days receive neurostimulation for 3 months (84 days, Period 1). If patients do not respond to stimulation as defined in the protocol on Day 42 and/or 56, the number of stimulations may be increased, including introducing stimulation during the night. Day 1 assessments (start of stimulation) will be used as baseline. At the end of Period 1 (Day 84), all patients will enrol into a long-term follow up (LTFU), Period 2. In Period 2, the management of drugs and stimulation parameters will be adjusted based on the level of disease activity and symptoms experienced by participants in consultation with the Principal Investigator (PI) or delegate and the Field Clinical Engineer (FCE). The safety, tolerability and efficacy of stimulation when used in conjunction with standard of care therapies, including conventional synthetic (cs)DMARDs with or without biologic (b)DMARDs or targeted synthetic (ts)DMARDs will be assessed. Participants who no longer wish to receive stimulation will have their IPG set in hibernation mode, return all accessories, and be followed for safety of the implant. If at some time during the 5-year follow-up period they want to restart stimulation this will be an option after discussion with the Principle Investigator (PI), or delegate, and FCE. The study will continue until the last participant entered has completed the 60 months visit in Period 2.
Galvani Splenic neuromodulation System:	The implantable system is designed specifically for laparoscopic delivery to the splenic NVB using Surgical Tools and Accessories. The lead is attached to an Implantable Pulse Generator (IPG) which will be inserted intraperitoneally and placed in the fat-pad connected to the falciform ligament. The lead and the IPG are referred to as the 'implantable system'. Non-implantable components of the System include a Clinician Programmer (CP), a Patient Remote (PR) and IPG Charger, a charging belt and adhesive patches to hold the IPG Charger over the IPG. The total system (including implantable and non-implantable components) is called the 'Galvani Splenic Neuromodulation System'. For the purposes of this protocol the term 'Galvani System' shall be used in reference to the 'Galvani Splenic Neuromodulation System'. All components of this system are considered investigational.
Objectives and Endpoints:	

Primary Period 1	
To evaluate the safety and tolerability of the Galvani System, its implantation, and subsequent stimulation of the splenic NVB.	- Incidence, causality and severity of Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Device Effects (ADEs) and Serious Adverse Device Effects (SADEs) - Laboratory Safety Assessments (clinical chemistry and haematology) - Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature) 12-Lead ECG monitoring
Secondary Period 1	
To evaluate the effect of splenic NVB stimulation on the change in pharmacodynamic and response biomarkers.	Changes from baseline (Day 1) in the levels of LPS-inducible cytokine/ chemokine release, including TNFα, IL-6, IL-8 and IL-17, in whole blood assay at 4 hours, Day 7, 14 and 84 after start of stimulation.
To assess the usability of the clinician and patient external devices.	Participants feedback on the use of CP, PR, Charger, Belt and Adhesive patch using Sponsor developed questionnaires.
To evaluate participants perception of therapy.	Participant's feedback using a sponsor-developed questionnaire.
To assess the device performance.	Tabulation of device deficiencies (DD).
Primary Period 2	
To evaluate the long term safety and tolerability of a chronic implant and if applicable, active stimulation of the splenic NVB with the Galvani System when used in conjunction with standard of care therapies including csDMARDs, with or without bDMARDs or tsDMARDs.	- Incidence, causality and severity of Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Device Effects (ADEs) and Serious Adverse Device Effects (SADEs). - Laboratory Safety Assessments (clinical chemistry and haematology). - Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature). 12-Lead ECG monitoring.
Secondary Period 2	
To assess the long-term usability of the clinician and patient external devices.	Patient and clinicians' feedback on the use of the Clinician Programmer (CP), Patient Remote (PR), Charger, Belt and Adhesive patch using sponsor-developed questionnaires.
To evaluate participants perception of therapy.	Participant's feedback using a sponsor-developed questionnaire.

To assess the device performance.		Tabulation of device deficiencies.
Study Population:	Adult patients with moderate to severe active RA who have an Inadequate Response (IR), or are intolerant, to at least two biologic Disease Modifying Anti-Rheumatic Drug (DMARD) or janus kinase inhibitor (JAKI) and who have undergone a sufficient wash-out period as defined in the protocol. Patients who are using a stable dose of a conventional synthetic DMARD or combination of those (e.g., methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide) or prednisolone, but are having an IR, are allowed to use this medication as background therapy.	
Population Size:	A maximum of 5 patients will be implanted in the trial.	
Phase:	Pilot Study	
Number of Investigative Sites:	The study will be performed at maximal 3 sites across the UK and the Netherlands.	
Study Duration:	The total expected duration of participation for the primary study period for each participant is approximately 5 months. This will include a 6-week screening period, a minimum of 4 weeks recovery from surgery, and 12 weeks of active treatment (see Figure 6 for study outline). Following the primary study period, participants will be followed in a long-term follow-up study (Period 2) which has a duration of 5 years.	

2. INTRODUCTION

The Galvani System consists of a lead, rechargeable implantable pulse generator (IPG), external components and accessories. The system is designed to deliver electrical stimulation to the splenic neurovascular bundle (NVB) in patients with rheumatoid arthritis (RA) or other inflammatory diseases.

2.1. STUDY RATIONALE

The study is designed to investigate the safety, tolerability, and provide an initial assessment of the effect of changed scheduling and number of stimulation episodes per day for participants with RA. An additional exploratory objective is to ascertain the mechanism by which splenic nerve stimulation affects RA, and to identify potential biomarkers that indicate response to splenic nerve stimulation.

2.2. BRIEF BACKGROUND

2.2.1 RHEUMATOID ARTHRITIS

Rheumatoid arthritis is the most common chronic autoimmune disease of the joints affecting close to 0.5-1.0% of the general population, with three times more women being affected than men. Patients present with painful, swollen and stiff joints and fatigue (Stack *et al.*, 2013). The pain and swelling of joints, or arthritis, is caused by synovial inflammation, the persistence of which leads to bone erosions, cartilage damage and finally joint deformities (McInnes & Schett, 2017). Virtually all peripheral joints can be affected by RA, although the most commonly affected joints are those of wrists, hands, knees, and feet. Rheumatoid arthritis is associated with a high risk for morbidity and premature death secondary to the earlier development of cardiovascular, lung diseases and malignancy (Young and Koduri, 2007). Common measures of RA disease activity are patient questionnaires regarding pain and daily activities, counts of swollen and/or tender joints, and laboratory test measurements of certain proteins (inflammatory markers). Patients with RA are at increased risk of developing cardiovascular disease, and the mortality rate is 1.5-1.6 fold higher compared to the general population (Sokka, Abelson and Pincus, 2008).

RA is classified according to the American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) 2010 classification criteria, which includes the number of joints involved, presence of serum autoantibodies, elevated inflammatory serum markers and duration of symptoms (Aletaha *et al.*, 2010).

The RA population is very heterogeneous, and the development of disease symptoms depends on a variety of genetic (susceptibility genes, epigenetic modifications) and environmental factors (smoking, obesity, changes to the microbiome of the mouth and gut). Together, these factors elicit immune responses, leading to inappropriate and robust immune cell proliferation, differentiation, and autoantibody production, which stimulate and maintain the inflammatory cascade in the synovium. This can occur through multiple molecular pathways that involve signaling through pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF α) and interleukin-6 (IL-6). The variety of molecular inflammatory pathways activated in RA patients may determine each individual's response to treatment, as recently approved therapies for RA treatment are molecularly targeted.

The recommended gold standard for treatment of patients with a confirmed RA diagnosis is methotrexate (MTX), which may be combined with other conventional disease modifying anti-inflammatory drugs (DMARDs) and/or corticosteroids. If disease activity cannot be controlled by conventional treatment, biological or targeted synthetic treatments are indicated. During the last decade, anti-cytokine biologics, such as anti-TNF α and anti-IL-6 receptor antibodies, became widely used for treatment of RA and have significantly improved disease outcome. Other treatments that have become available in the past years are strategies interfering with B-cells (rituximab) and costimulatory pathways (abatacept), and Janus kinase inhibitors (JAKI) (e.g., upadacitinib, tofacitinib) (Nakayamada *et al.*, 2016; Smolen *et al.*, 2017; Harrington, Al Nokhartha and Conway, 2020).

Despite the fact that there are many types of DMARDs available, only a minority of patients reach the treatment goal of remission or low disease activity (Smolen, Alethaha & McInnes, 2016). At any time, >50% of patients will still have active disease. Besides the lack of response to therapy, patients discontinue medication because of side effects, including increased risk of opportunistic infections, neurological events, immune and autoimmune responses, or because they do not want to take chronic medication (Sakai *et al.*, 2012). As a result, the need for the development of new therapeutic strategies remains.

2.2.2 SPLENIC NERVE STIMULATION

Neuromodulation has been suggested as a potential treatment option for patients suffering from RA (Koopman *et al.*, 2017). Studies have shown that the autonomic nervous system (ANS) can, through the sympathetic and parasympathetic systems, influence development and severity of inflammation in animal models (Koopman *et al.*, 2011). Previous work has suggested an imbalance of the ANS in established RA (Adlan *et al.*, 2014). This imbalance could be the result of chronic inflammation, but conversely it is also possible that changes in the ANS influence inflammation, disease development and severity. Vagus nerve stimulation (VNS) has demonstrated early feasibility and potential to improve clinical outcomes while reducing pro-inflammatory cytokines in patients with RA (Koopman *et al.*, 2016; Genovese *et al.*, 2020). VNS also improved RA disease severity in some patients with therapy-resistant disease. VNS exerts its potential immunomodulatory effects indirectly, relying on evoking neural signals in vagal fibers to the celiac ganglion where in turn signaling may be triggered in adjacent adrenergic neurons projecting to the spleen (Kressel *et al.*, 2020). However, the vagus nerve also controls most, if not all, organs of the body, and therefore many off target effects such as bradycardia can occur and such effects are expected to strictly limit or prevent a VNS therapeutic window (i.e., the stimulation parameter range in which immunomodulatory effects can be achieved without side effects).

The spleen has been shown in animal models to be the principal organ for neuronal regulation of systemic inflammation (Rosas-Ballina *et al.*, 2008). In addition, it has been confirmed that direct Splenic Nerve Stimulation (SpNS) is as effective as VNS in models of endotoxemia and arthritis without the significant cardiovascular off-target effects seen there for VNS (Guyot *et al.*, 2019; Vida *et al.*, 2011). Hence, stimulating the splenic nerve directly in patients with RA may more robustly and reliably activate the splenic immunomodulatory effects without the bradycardia, laryngeal muscle contraction, and other tolerability limitations of VNS. Evidence from small and large animal models, studies in porcine and human tissue and immune cells, and a pilot clinical study have provided

extensive evidence of immunomodulatory effect from SpNS and suggests it differs from biological or targeted synthetic DMARDs (b/ts DMARDs).

The therapeutic potential of splenic nerve stimulation was demonstrated in several preclinical disease models by Galvani Bioelectronics and its collaborators (see the Investigator's Brochure (IB) for more detail). Stimulation of the splenic nerve in mice resulted in norepinephrine release from nerve terminals within the spleen (Guyot *et al.*, 2019). The binding of noradrenaline (NA) to adrenergic receptors (beta-1 and beta-2) on the surface of immune cells was shown to impact pro-inflammatory monocyte populations and modulated the release of TNF α . Splenic nerve stimulation also prolonged survival in both an acute lipopolysaccharide (LPS) -induced inflammatory model in pigs (Donega M, Fjordbakk C.T., Kirk, J, Sokal D et al., (2021). Human-relevant near-organ neuromodulation of the immune system via the splenic nerve. PNAS, Vol 118. No.20 *et al.*, submitted for publication), as well as an endotoxemia model in mice (Guyot *et al.*, 2019). Preclinical experiments in a mouse model of arthritis demonstrated that chronic splenic NVB stimulation was able to protect mice from development of disease when delivered in a prophylactic manner (Simon *et al.*, 2020). This was accompanied by a reduction in serum TNF α levels and number of inflammatory monocytes in the spleen which correlated with the clinical scores. In addition, splenic stimulation suppressed the expansion of splenic B lymphocytes in the spleen and reduced anti-collagen autoantibody production. Stimulating six times a day was more effective compared to stimulating once a day, providing an indication of dosing regimen. Evaluating stimulation during either the resting or active period in mice demonstrated that stimulation during the active period was almost as effective in decreasing the clinical scores as stimulation over a 24 hour period however not as effective in fully suppressing incidence of disease (see IB). More importantly, starting treatment after onset of disease showed a significant reduction in clinical scores and this was even further potentiated by combination treatment with etanercept (Simon *et al.*, 2020).

Suppression of LPS-triggered inflammation in pigs provided large-animal *in vivo* proof of concept using the Gen-1 system and the dosing strategy intended for the clinic. These studies showed NA release in the spleen and reduced production of TNF α , IL-6, and kynurenines; all known inflammatory mediators in RA. Further, the cellular metabolism in monocytes from the stimulated pigs was diverted away from inflammatory conditioning, and metabolites known to exacerbate inflammation were reduced. SpNS was also shown to upregulate specialised pro-resolving mediators (SPMs), including Resolvin D1 and D3, known to promote cessation of inflammation and initiation of tissue healing. Importantly, SpNS was shown to not be immunosuppressive in healthy stimulated pigs with inflammatory responses in peripheral blood maintained when stimulated *ex vivo* with LPS.

Pig and human *in vitro* splenocytes studies demonstrated that the immunomodulatory effects were driven by the binding of NA to beta adrenergic receptors on monocytes residing in the spleen, modulating transcription and release of multiple cytokines (including TNF α , IL-6, CCL2, IL-1 β , and IL-10) via phosphoinositide 3-kinase intracellular signaling mechanisms and through post transcriptional changes in the NLRP3 inflammasome. Beyond monocytes, NA reduces cytokine release (including IFN- γ and IL-17A), and SPMs were upregulated and released from these leukocytes (see the IB for more detail).

Finally, application of SpNS intraoperatively during laparoscopic esophagectomy in cancer patients was shown to reduce the inflammatory marker, C-reactive protein post-surgery.

Taken together, the evidence suggests SpNS differs from biological or targeted synthetic disease-modifying anti-rheumatic drugs (b/ts DMARDs) in three key ways, providing the scientific rationale for assessing its safety, tolerability, and therapeutic potential in RA patients with inadequate response (IR) to prior treatments:

- SpNS is immunomodulatory, reducing pathological inflammatory responses while maintaining a healthy inflammatory response, rather than completely blocking specific cytokines and other specific pathways that b/ts DMARDs inhibit.
- SpNS affects multiple mechanisms often pathological in RA patients, which may provide wider and additive efficacy compared to inhibition of a single pathway with a b/ts DMARD that typically induces disease remission only in a subset of patients
- SpNS up-regulates pro-resolving mediators and promotes inflammatory cell reprogramming that may shift the immune system balance from pro-inflammation to inflammation resolution

2.2.3. THE GALVANI SYSTEM IMPLANTED AND NON-IMPLANTED COMPONENTS

The Galvani System is a single lead, rechargeable neurostimulation system designed to deliver electric stimulation to the splenic neurovascular bundle in participants with active RA. The Galvani System is shown in **Figure 1**.



Figure 1: Galvani System. A: IPG, B: Lead, C: Cuff Electrode, D: Clinician Programmer (CP), E: Patient Remote (PR), F: IPG Charger

The implanted components (“Implantable System”) consist of an IPG and a lead, which are implanted into the abdominal cavity of the patient through a laparoscopic procedure using surgical tools and accessories. The IPG is secured to the anterior abdominal wall and a pocket created in the fat pad associated with the falciform ligament, caudal to the sternum using permanent trans fascial sutures.

The rechargeable IPG is the source of neurostimulation for the Galvani System. The IPG is connected directly to the lead to supply a single channel of bipolar stimulation to the splenic neurovascular bundle. The IPG communicates with the non-implanted devices using Bluetooth® Low Energy (BLE) as well as an inductive link for certain commands. It is powered by a rechargeable battery which minimises the size of the IPG and prolongs the lifespan of the system. The size and features designed into the IPG support laparoscopic implantation into a pocket created in the tissue associated with the falciform ligament on the inside of the abdominal wall. This placement reduces the risk of leads being damaged by trauma, minimises the chance of the devices flipping due to physical movement or patient manipulation (i.e., twiddler's syndrome) and may further minimise pocket infections as contact between the skin is avoided in the implant procedure. The IPG has a number of safety features designed to decrease patient risk, including internal self-checks and protection circuitry.

The IPG delivers stimulation as programmed by the CP. Therapy delivery is programmed using various parameters and is scheduled to be delivered a number of times per day using a scheduling function. The internal software in the IPG is upgradable using the wireless communication link. The IPG has embedded memory which is used to keep all therapy parameters as well as use logs and history and diagnostic information.

The lead consists of a lead body with a distal end cuff electrode applied to the splenic neurovascular bundle, and a proximal connector connected to the IPG (

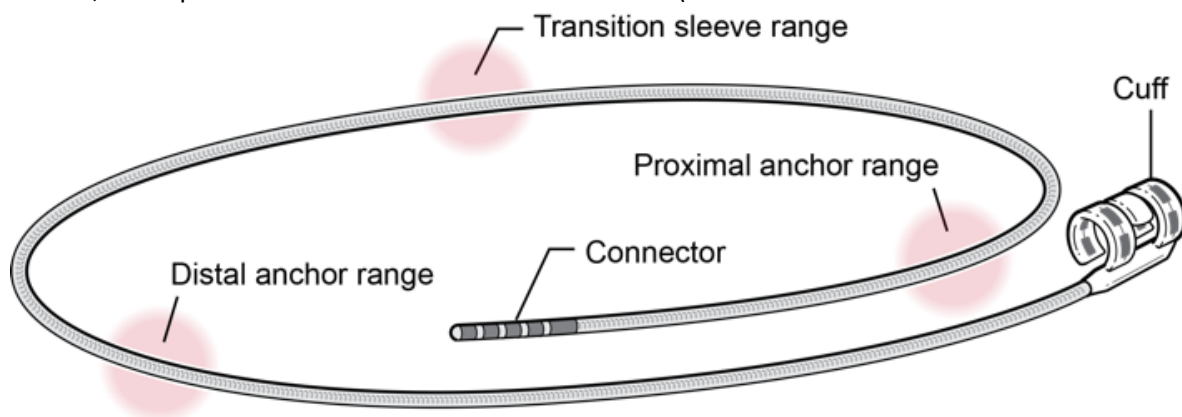


Figure 2). The lead is manufactured from traditional implant grade silicone, polyurethane, and metals. The design is specific to support laparoscopic implantation for cuff placement around the splenic neurovascular bundle. The lead is anchored permanently to the crus of the diaphragm and the anterior abdominal wall to absorb visceral movements.

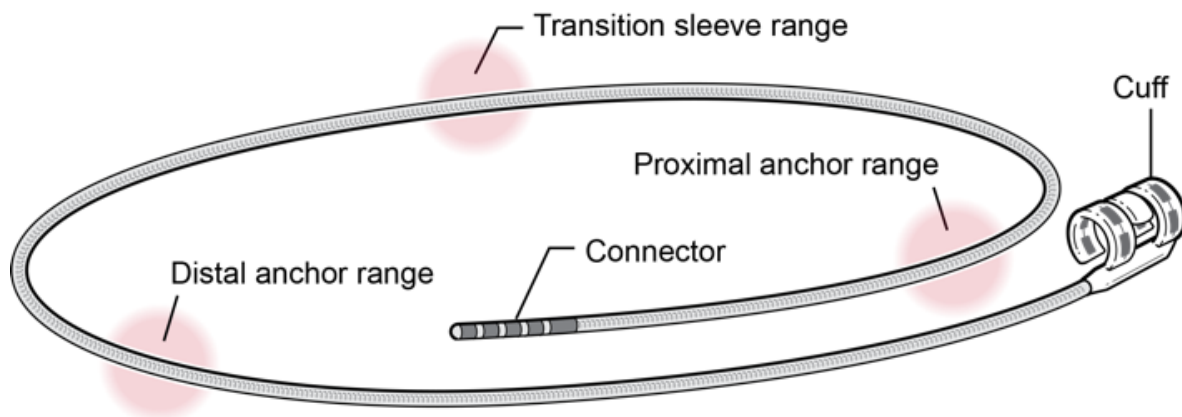


Figure 2. Implantable lead and cuff

The cuff is designed to interface with nerves located around the periphery of the splenic artery. The cuff is available in two sizes to accommodate variability of the splenic NVB (small and medium) and contains two electrically active electrode arms and one inert middle arm to aid in cuff retention around the splenic artery. The cuff includes a deployment tab to assist in the surgical application around the neurovascular bundle (Figure 3). The tab is removed and discarded once the cuff placement is confirmed.

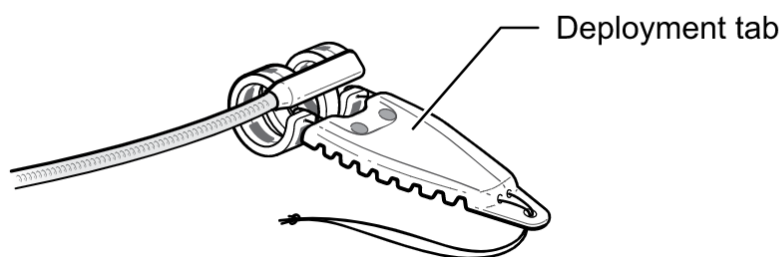


Figure 3. Cuff electrode with deployment tab

The Galvani System is accompanied by surgical tools and accessories consisting of an oblong trocar to allow the introduction of the IPG into the abdominal cavity, a lead cap, a torque wrench, and a delivery cannula to allow the introduction of the lead into the abdominal cavity (Figure 4 and Figure 5).

Surgical tools and accessories

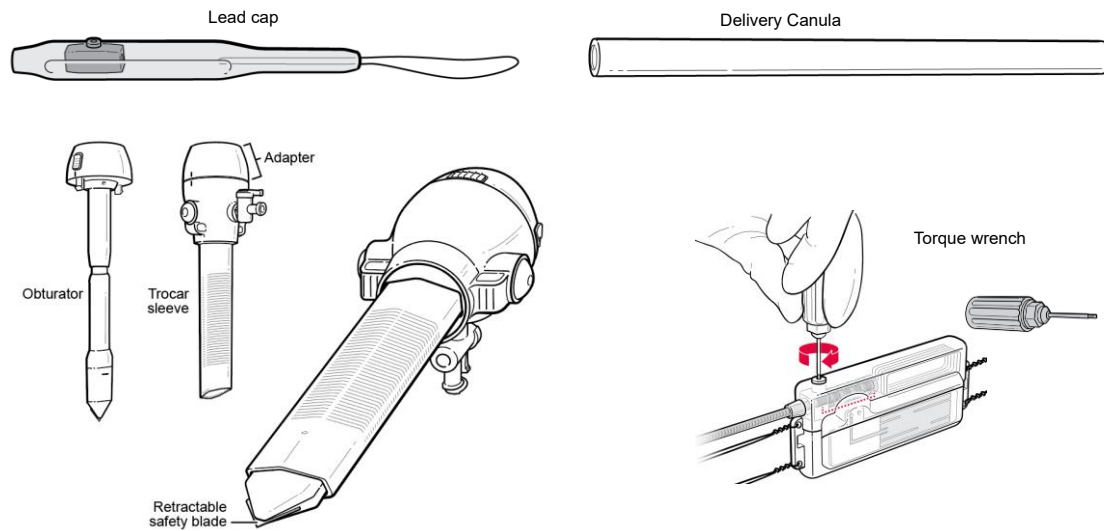


Figure 4. Surgical tools and accessories

Final implant location

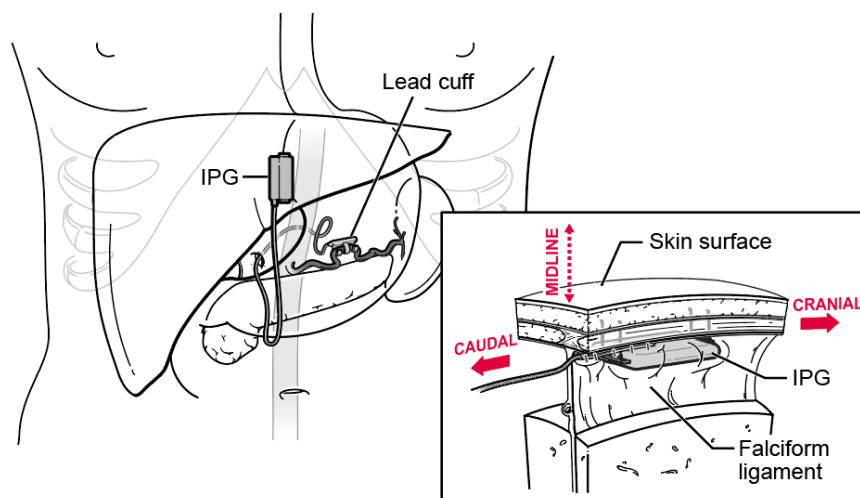


Figure 5. Schematic of implanted lead and IPG

The Galvani System implantation is a laparoscopic procedure involving cuff placement around the splenic neurovascular bundle, anchoring of the lead to the right crus of the diaphragm and fixation of the IPG in the fat pad associated with the falciform ligament.

The non-implanted provider-facing device is the CP implemented on a Samsung tablet (Figure 1), used to manage the implant and therapy parameters through an expanded set of functions that allow full

programmability of the implant settings and configuration of certain functions available to the patient on the PR. The CP is also used to test the implant system as part of the implantation procedure. The CP includes an AC power adapter.

The non-implanted patient-facing devices are the PR implemented on a Pixel smartphone and the IPG Charger (Figure 1) with accessories. The PR is used to manage therapy and interact with the implantable components through a limited set of functions, some of which are only configurable by the clinician. The PR includes an AC power adapter. The IPG Charger is used for recharging the IPG battery and includes two accessories: adhesive patches and a charging belt for holding the IPG Charger in place during charging sessions. The IPG Charger doubles as a security token for BLE registration of the IPG with the CP and the PR. As an additional safety feature, the PR and IPG Charger can also be used to disable therapy. The IPG Charger includes an AC power adapter as well.

3. OBJECTIVES AND ENDPOINTS

3.1. PRIMARY OBJECTIVES AND ENDPOINTS PERIOD 1

The primary objective and endpoints are:

1. To evaluate the safety and tolerability of the Galvani System, its implantation, and subsequent stimulation of the splenic NVB as assessed by:
 - a. Incidence, causality and severity of Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Device Effects (ADEs) and Serious Adverse Device Effects (SADEs).
 - b. Laboratory Safety Assessments (clinical chemistry and haematology).
 - c. Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature).
 - d. 12-Lead electrocardiogram (ECG) monitoring.

3.2. SECONDARY OBJECTIVE AND ENDPOINTS PERIOD 1

The secondary objectives and endpoints are:

1. To evaluate the effect of splenic NVB stimulation on the change in pharmacodynamic and response biomarkers as assessed by:
 - a. Changes from baseline (Day 1) in the levels of LPS-inducible cytokine/ chemokine release, including TNF α , IL-6, IL-8 and IL-17, in whole blood assay at 4 hours, Day 7, 14 and 84 after start of stimulation.
2. To assess the usability of the clinician and patient external devices as assessed by:
 - a. Patient and clinicians' feedback on the use of CP, PR, Charger, Belt and Adhesive patch using sponsor-developed questionnaires.
3. To evaluate participant's perception of therapy as assessed by:
 - a. Participant's feedback using a sponsor-developed questionnaire.
4. To assess the device performance as assessed by:
 - a. The tabulation of device deficiencies (DD).

3.3. EXPLORATORY OBJECTIVES AND ENDPOINTS PERIOD 1

The exploratory objectives and endpoints are:

1. To evaluate the efficacy of splenic NVB stimulation on clinical signs and symptoms as assessed by:

- a. Change from baseline (Day 1) in the Simple Disease Activity Index (SDAI) at Day 14, 28, 42, 56, 70, and 84
- b. Change from baseline in DAS28-CRP at Day 14, 28, 42, 56, 70, and 84.
- c. Change from baseline in Clinical Disease Activity Index (CDAI) at Day 14, 28, 42, 56, 70, and 84
- d. nACR improvement (=lowest % improvement of tender joint, swollen joint, and 3/5 remaining measures) Day 84.
- e. Proportion of participants achieving a moderate/good EULAR response at Day 84.
- f. Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) score at Day 14, 28, 56 and 84
- g. Change from baseline in physical and mental component scores and domain scores of SF-36 at Day, 28, 56 and 84
- h. Change from baseline in quality of life as measured by Rheumatoid Arthritis Impact Disease Questionnaire (RAID) at Day 14, 28, 56 and 84.

Note: For composite endpoints each component of the assessment will also be reported. The changes over time will also be reported.

2. To evaluate the effect of intraoperative splenic NVB stimulation on target engagement as assessed by:
 - a. Impedance as measured by the IPG before and after stimulation.
 - b. Measurement of the heart rate (HR) before, during and after stimulation.
 - c. Measurement of the mean systolic blood pressure (MSBP) before, during and after stimulation.
3. To evaluate signatures of dysregulated immune responses that predict treatment responses, and changes in signatures that occur during treatment as assessed by:
 - a. Change from baseline (Day 1) in inflammatory mediators (including but not limited to TNF α , IL-6, IL-8, and IL-17), resolvins (including but not limited to RvD1, RvD3, PD1, Mar1 and PGE2), and factors involved with cartilage and bone catabolism/metabolism in plasma samples at Day 7, 28, and 84.
 - b. Change from baseline (Day 1) in distribution and phenotypes of cell subsets in whole blood at Day 7, 28 and 84.
 - c. Change from baseline (Day 1) on immune phenotyping by multi-parameter flow cytometric analysis and *ex vivo* stimulation assays to evaluate e.g., epigenetic and phospho-protein (e.g., STAT3, STAT6) changes in different cell subsets at Day 28 (excluding epigenetic changes) and 84.

3.4. PRIMARY OBJECTIVE AND ENDPOINT PERIOD 2

1. To evaluate the long term safety and tolerability of chronic implant and if applicable active stimulation of the splenic NVB with the Galvani System when used in conjunction with standard of care therapies including csDMARDs, with or without bDMARDs or tsDMARDs.

- a. Incidence, causality and severity of AEs, SAEs, ADEs and SADEs.
- b. Laboratory Safety Assessments (clinical chemistry and haematology).
- c. Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature).
- d. 12-Lead ECG monitoring.

3.5. SECONDARY OBJECTIVES AND ENDPOINTS PERIOD 2

- 5. To assess the usability of the clinician and patient external devices as assessed by:
 - b. Patient and clinicians' feedback on the use of the Clinician Programmer (CP), Patient Remote (PR), Charger, Belt and Adhesive patch using sponsor-developed questionnaires.
- 6. To evaluate participant's perception of therapy as assessed by:
 - a. Participant's feedback using a sponsor-developed questionnaire.
- 7. To assess the device performance as assessed by:
 - a. The tabulation of DDs.

3.6. EXPLORATORY OBJECTIVES AND ENDPOINTS PERIOD 2

- 1. To determine whether the participants who achieved an initial clinical response to stimulation in Period 1 (as defined by > 1.2 improvement in DAS28-CRP at week 12 versus baseline Day 1 in Period 1), but failed to achieve a $\text{DAS28} \leq 2.6$, can improve clinical response upon stimulation for an additional 12 weeks as assessed by:
 - a. Achieving a $\text{DAS28-CRP} \leq 2.6$ at Month 3 of the LTFU Period 2.
- 2. To determine whether the participants who did not achieve a clinical response to stimulation in Period 1 (as defined by < 1.2 improvement in DAS28-CRP at week 12 versus baseline Day 1 in Period 1) can improve clinical response by adding a cs, ts or bDMARD medications in addition to the stimulation therapy, as assessed by:
 - a. Achieving a $\text{DAS28-CRP} \leq 2.6$ at Month 6 of the LTFU Period 2.
- 3. To evaluate the efficacy of splenic NVB stimulation on clinical signs and symptoms as assessed by:
 - i. Change from baseline (Day 1 Period 1) in the DAS28-CRP, Simple Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) at assessment points.
 - j. nACR improvement (=lowest % improvement of tender joint, swollen joint, and 3/5 remaining measures) at assessment timepoints compared to baseline Day 1 Period 1.
 - k. Proportion of participants, which are stimulating, achieving a moderate/good EULAR response at Month 60.
 - l. Change from baseline (Day 1 Period 1) in Health Assessment Questionnaire Disability Index (HAQ-DI) score at assessment timepoints.
 - m. Change from baseline (Day 1 Period 1) in physical and mental component scores and domain scores of SF-36 at assessment timepoints.
 - n. Change from baseline (Day 1 Period 1) in quality of life as measured by Rheumatoid Arthritis Impact Disease Questionnaire (RAID) at assessment timepoints.

Note: For composite endpoints each component of the assessment will also be reported. The changes over time will also be reported.

1. To evaluate biomarkers involved with cartilage and bone catabolism/metabolism as assessed by:
 - a. Change from baseline (Day 1 Period 1) at study assessment timepoints.
2. To evaluate biomarkers of efficacy which will be defined and selected from Period 1 as assessed by:
 - a. Change from baseline (Day 1 Period 1) at study assessment timepoints.

4. STUDY DESIGN

4.1. OVERALL DESIGN

The study will be an open label single arm study to evaluate the safety and tolerability of Galvani's neuromodulation system. The total study duration for each participant is approximately 5 months in Period 1 and 5 years in Period 2.

Period 1 will consist of a 6-week screening period, 4 weeks recovery from surgery and a 3-month 'treatment' period. Implant procedures will be temporarily halted after the first participant. Once this participant reaches Day 14 of stimulation, a Data Safety Monitoring Board (DSMB) will evaluate any adverse events and adverse device effects and will recommend either to continue implant procedures or other actions. Participants may have stimulus amplitude increased (dose escalated) during all visits to Day 28 (Days 1, 4, 7, 14, and 28).

The participants will return to the clinic on pre-defined days for follow-up visits during the trial period. At Days 42 and/or Day 56, if the DAS28-CRP is > 2.6 on the day of visit, the number or timing of stimulations will be adapted according to the following order:

- If participants do not experience a discomfort during stimulation the number of stimulations (6) will be divided over day and night-time (i.e. 6 stimulations over 24 hours).
- In participants where night-time stimulation is introduced and who are still having a DAS28-CRP > 2.6 at the next visit (Day 56), additional 6 stimulations (resulting in a total of 12 stimulations) equally divided over the 24 hours will be added.
- If participants are experiencing a discomfort/sensation and will not tolerate night-time stimulation, the number of stimulations during daytime will be increased to a maximum of 12 during daytime if the DAS28-CRP > 2.6 on Day 42 or Day 56.

Period 2 will evaluate the long term safety, tolerability and efficacy of the Galvani System. All participants will stay in Period 1 until Day 84 to evaluate safety even if the stimulation is switched off. The study will continue until the last patient has completed the 60 months visit of Period 2. Participants who no longer wish to receive stimulation will have their IPG set to hibernation, return all accessories, and be followed for safety. If at some time during the 5-year follow-up period participants want to restart stimulation since they have a permanent implant, e.g. if they are partial responders to their new initiated b or ts DMARD and they want to try to reduce the disease activity further by adding stimulation on top of the treatment, this will be an option after discussion with the PI, or delegate, and FCE.

Follow-up visits for participants with stimulation ON will occur every month for the first 3 months, then every 3 months for the first 2 years and thereafter every 6 months after they start in Period 2. Participants with the device in hibernation mode will be followed for safety and device related AEs every 6 months for 5 years, after start of Period 2 (last visit of Period 1/Day 1 Period 2). Participants are allowed to restart stimulation at any time during Period 2 to support their standard of care treatment in consultation with the PI or delegate and FCE. A ramp-up schedule will be followed similar to start of therapy in Period 1. An Interim visit must be performed a maximum of 1 month after any change in device settings. Additional unscheduled visits may also be performed at any time at the principal investigator's discretion; either between scheduled visits, or after the patient has completed the Month 60 Visit, if the study is still ongoing. Safety evaluations will be performed for all participants at every on-site visit whereas efficacy assessments will only be performed in participants undergoing stimulation.

The management of drugs and stimulation parameters may be adjusted based on the level of disease activity and symptoms experienced by the participants. The safety, tolerability and efficacy of stimulation when used in conjunction with standard of care therapies, including csDMARDs and with or without bDMARDs or tsDMARDs, in pursuit of the treat-to-target therapeutic goal will be assessed. Participants may adjust the stimulation parameters in relation to amplitude (max 20 mA) and number of stimulations a day (max 12), following the schedule as described in section 6.5, but additional options can be discussed with, and will be changed on the discretion of the PI, or delegate, and FCE.

4.2. STUDY SCHEMATIC

A schematic presentation of the study design is shown in Figure 6.

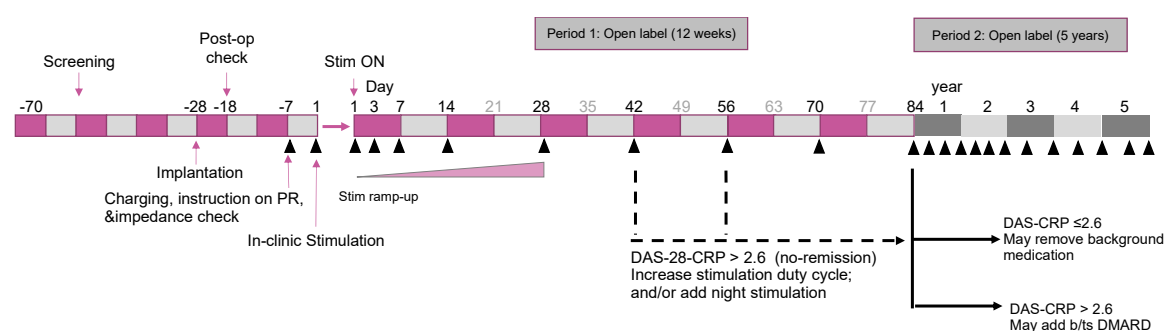


Figure 6. Study timeline: After signing the Informed Consent (IC), participants will be screened. If enrolled in the study all participants will be implanted with the implantable system (IPG and Lead). After recovery, all participants will start stimulation. If at Day 42 and/or 56 the participants are not in remission, the number or timing of stimulations will be adapted. At the end of the study (Day 84), the participants will proceed to the long-term follow-up (LTFU; Period 2). Filled triangles – in person visits. *High level overview of Period 2 see Section 6.4.

A detailed schedule of procedures and activities for Period 1 and Period 2 can be found in Section 6.1, Table 3, Table 4, Table 5, Table 6, Section 7.1 and Table 7, respectively. A brief description of the study is described in the next paragraphs.

4.2.1. SCREENING AND IMPLANT

- After informed consent, participants will be assigned a unique participant number and screened by investigators for eligibility. Screening will include a minimum of two visits, one with the investigator rheumatologist and one with the implanting surgeon. The screening period (including waiting time for the surgical procedure and washout time for b/tsDMARDS) can take up to 6 weeks but might be shortened if feasible.
- The rheumatologist (investigator) will assess the participants ability to perform the procedures required to operate the Galvani System (the ability to use a smart phone, to connect the charging cable to phone, and to remove backing from sticky patches or put a belt on). In addition, an ultrasound will be performed as an initial step in screening for verification of abdominal wall thickness (AWT) (epidermis to posterior rectus sheath). If the AWT is ≤ 2.5 cm, this will be followed by the clinical assessments and safety laboratory assessments. The implanting surgeon (co-investigator) will perform additional tests including a pre-op clearance according to the local standards. A CT-angiography scan of the abdomen will be performed to confirm appropriate anatomy for the implant procedure, measure the artery lumen and AWT at the IPG implant location. If all screening criteria are met, the implant procedure will be scheduled.
- Participant taking bDMARDS or tsDMARDS will stop the medication 2 weeks before the surgery, except for rituximab which should already been discontinued by the participant 6 months before Day 1 (start stimulation).
- On the day of surgery (Day -28), the lead and IPG will be implanted using a laparoscopic procedure.
- During surgery, the lead will be placed around the splenic NVB and connected to the IPG. The system will be tested to verify appropriate function prior to the completion of surgery. In addition, two stimulation episodes may be delivered to collect surrogate cardiovascular biomarkers (HR and MSBP) for stimulation. The IPG will be placed in a pocket created in the pre-peritoneal fat pad associated with the falciform ligament. The IPG can also be placed in the subcutaneous space if required due to unexpected intraoperative anatomical findings. An X-ray will be taken immediate post-surgery to confirm that the cuff remains in the correct position after deflation of the abdomen. After completion, the device will be set to a non-active state. The procedure is expected to take approximately 1.5 to 2 hours after which the participant will stay overnight to monitor recovery. The following day (Day -27) the participant will undergo a post-op check by the surgeon or delegate before being discharged from hospital.
- The participant will be seen by the surgeon on postoperative day 10 (Day -18) to assess their recovery from surgery. In addition, data from the IPG (IPG log) will be collected by the FCE and reviewed (such as system impedance) to confirm correct placement and function of the system.
 - If the participant is found to have recovered from the surgical procedure, he/she will be referred to their rheumatologist for ongoing management according to the research protocol.
 - If the surgeon has any concerns, they will follow the participant until they determine that the participant has recovered from the procedure and can undergo initiation of neuromodulation therapy.
 - If IPG log data reveals any issue in relation to cuff position or function action will be undertaken to further evaluate the finding and follow up actions taken as described in the Manual of Procedures.

- If participants experience a flare in symptoms during the screening and recovery period that needs treatment, the physician can adapt the medication as indicated in Section 4.6 and 5.5.
- On Day -7, the participant will be seen by the FCE in the rheumatology office. Again, the IPG log data will be collected and the impedance will be checked to confirm proper function of the cuff. In addition, the participant will be instructed by the FCE on the use of PR and IPG charger followed by a charging session in the clinic.

4.2.2. PERIOD 1

Day 1 Visit

At least 28 days post implant, participants will visit the clinic (Day 1) and stimulation will be started. The stimulation amplitude will be increased (dose escalated) at this visit, based on participants' feedback on tolerability of dose escalations, at PI's discretion and in consultation with the sponsor.

- On the Day 1 visit all baseline assessments will be performed (see Section 7 for details).
- The FCE will start the step-up of the stimulation. The stimulus amplitude will be increased from 1 mA to a percentage of a predefined target amplitude in increments of 1 mA or 0.5 mA, or to a maximum tolerable dose (MTD). An illustration of programming during these first visits is shown in Figure 7. and in detailed described in Section 7.8.2.
- Blood will be drawn before and after the stimulation session, to assess the time course of any biological response.
- At the end of the visit, the Galvani System will be programmed to automatically apply stimulation therapy.
- Prior to leaving the clinic, all participants will be re-instructed on the use of the PR and charger by the FCE. The IPG charger and the PR can both be used to turn off the system in case of an emergency and in this case, participants will have to visit their physician to have stimulation re-initiated.

Visit Days 4, 7, and 14

- Stimulus amplitude will continue to be incremented in a similar fashion as on day 1 starting each day from the final amplitude programmed on the previous visit, up to the day's target dose (or MTD) in increments of 1 mA (see Section 7.8.2 and Figure 7). If the maximal amplitude (20 mA) is reached at day 7 no step-up stimulations will be performed at Day 14. All other assessments and biomarker analysis as indicated in the Study Schedule Section 7.1 will still be performed.

Visit Days 28, 42, 56, 70 and 84

- During all visits to Day **56** the participant's stimulus amplitude may continue to be incremented in a similar fashion as on day 1 starting each day from the final amplitude programmed on the previous visit, up to the day's target dose (or MTD) in increments of 1 or 0.5 mA (see Section 7.8.2 and Figure 7). If the maximal amplitude (20 mA) is reached **before** Day 56, no step-up stimulations will be performed at subsequent visits in Period 1.

- Clinical and safety assessments and laboratory safety assessments will be performed, and samples for biomarker studies will be collected as indicated in the Study Schedule in Section 7.1.
- If on Day 42 the participant has not reached remission as defined by a DAS28-CRP > 2.6 (no remission), night-time stimulation might be introduced as described in Section 4.1 and the Manual of Procedures. If on Day 56 the participant has not reached remission, the number of stimulations over 24 hours will be further increased to 12 stimulations total. If night stimulation was added but the participant does not tolerate this, the number of stimulations may be increased to 12 over the day time.
- If on Day 42 the participant has not reached remission and night stimulation will not be tolerated due to sensation, the number of stimulations will be increased to 12 stimulations during day time.
- At the end of Period 1, participants will proceed to the long-term follow-up (LTFU) Period 2 (see Section 6.4).

4.2.3. PERIOD 2

Period 2 should start on the same day as the last visit of Period 1, Day 84. After the Day 84 assessments are performed a CT-angiogram will be taken (4 months post implant) within 2 weeks from Day 84.

At the discretion of and after discussion between the PI, or delegate, and FCE, based on level of the disease activity at the visit, stimulation parameters may be increased or decreased (see also section 6.5 and 6.6). In addition, at the discretion of the PI or delegate, the RA standard of care medication may be adapted.

Month 1 to Month 60 Visits Period 2

At the Month 1 to Month 60 Visits, the following assessments will be performed according to the schedule of activities in Table 7:

Safety Evaluations (all participants):

- Physical Examination
- Vital signs
- 12 Lead ECG
- Laboratory Safety assessments
- AEs, ADEs and DDs
- Abdominal duplex ultrasound (month 12, 30 and 60)

PROs/Questionnaires/Disease Activity Assessments (participants receiving stimulation):

- Disease assessments
- HAQ DI
- RAID
- SF-36
- Device checks including impedance measurements*
- Device charging*

- Concomitant Medications as per Section 5.5.2.
- PROs/questionnaires
- Blood draws for biomarker analysis

Participants in which the device is in hibernation mode are followed for safety only and assessments described under safety evaluations will be performed. In patients having the device in SHAM mode the assessments marked with an * will be added to the safety evaluations.

At the discretion of and after discussion between the PI, or delegate, and the FCE, based on level of the disease activity at the visit, stimulation parameters that may be increased or decreased (see also section 6.5 and 6.6) at any visit. Allowable ranges for new parameters will be described in the Manual of Procedures.

At the discretion of the Investigator or delegate the RA standard of care medication may be adapted.

4.2.4. STAGGERED ENROLLMENT

Initially one participant will be implanted. After this participant has completed the Day 14, Period 1 visit any adverse events and adverse device effects will be evaluated by a DSMB, who will then recommend continuing with implant procedures, or other actions if needed before additional participants undergo surgery to implant the IPG and lead. Recruitment and screening may continue during this period.

4.3. DOSE JUSTIFICATION

In Period 1, all participants will be dose escalated to the pre-defined target dose of 20 mA at all visits to Day 28, based on participants' feedback on tolerability of dose escalations, at investigator's discretion and in consultation with the sponsor. The initial number of stimulation episodes will be six during daytime. The number of stimulations, to 12 in 24 hours, a day might be adapted during the trial and/or night-time stimulation might be introduced if participants do not experience a discomfort during stimulation (see Section 4.2.2 for details).

In Period 2, those participants on active stimulation at the time of starting Period 2, will continue on active stimulation at the same stimulus parameters or may adapt the stimulation as described in section 6.5 and 6.6. If participants have their stimulation OFF, they may start stimulation at any time during Period 2, at investigator's discretion and in consultation with the sponsor.

Detailed information and dose parameter justification regarding the proposed dosing and device parameters can be found in the IB.

4.3.1. INTRAOPERATIVE STIMULATION

Intraoperative stimulation during the implantation of the device while the abdomen is insufflated will be limited to two stimulations at, with at least a 5-minute rest period between. The stimulation can

be terminated on the surgeon's request. A ramp period will be added to each period of stimulation, which will bring the amplitude from 0 to the programmed amplitude. Based on pre-clinical human *ex vivo*, and prior clinical intraoperative data, these stimulation parameters should result in activation of the splenic nerves within the NVB, while also inducing contraction of the vessel smooth muscle, and giving rise to observable changes in electrical impedance as read from the CP. Measurements in heart rate and blood pressure will be recorded during these stimulation periods.

4.3.2. CHRONIC STIMULATION

Starting from Day 1 Period 1, a 5 min burst stimulation will be applied at the programmed amplitude, in which the burst stimulation is applied for 0.5 seconds, and then suspended (OFF) for 4.5 seconds (at 10 Hz frequency, 2 ms pulse width). Burst stimulation will be used during chronic treatment in participants as this results in immunomodulatory neural activation while reducing prolonged splenic smooth muscle contraction and potential systemic blood pressure changes. Each dose will incorporate a ramp up from zero to the desired output. Six doses of stimulation will be applied throughout the day two hours apart. If an increase in dose is desired to improve the clinical response (and participant's experience of the therapy is favorable) the number of stimulation episodes per day can be increased to 12, and/or night time stimulation episodes can be introduced (see Section 4.1 and 4.2.2). In addition, the stimulation can be further adapted in Period 2 (see section 6.5 and 6.6).

4.4. INCIDENTAL FINDINGS

Incidental findings identified with the ultrasound analysis, CT scan, during the surgical procedure or other study assessment will be reported to the PI. The PI will discuss the finding with the participant and in consultation with the participant's GP refer the participant to the appropriate specialised physician for further evaluation of the finding and standard of care treatment. The PI and/or surgeon will decide if the participant can continue in the study. Significant incidental findings at screening and during implant surgery will be recorded on the Medical History eCRF. Any other new findings during the study should be reported as AEs.

4.5. BENEFIT-RISK ASSESSMENT

In this single arm open label study, splenic nerve stimulation is delivered to participants with active RA. The primary objective is to assess the safety of splenic nerve stimulation, and the secondary objectives are to evaluate effects on biomarkers, usability, participant perception and device system performance. Efficacy on clinical signs and symptoms and further biomarkers will also be evaluated as part of exploratory objectives. While currently there are no data to support the efficacy of splenic nerve stimulation in patients with RA, animal models of arthritis and inflammation have shown that splenic nerve stimulation is associated with a reduction in inflammatory markers and a decrease in clinical signs and symptoms of arthritis when stimulation is started after onset of disease. In addition, animal model data suggest that there is a possibility that patients may have a reduction in disease activity, or the progression of disease may be slowed or halted. To determine whether these pre-clinical findings translate to improvement in signs and symptoms of RA, standard clinical assessments will be made, like a joint stiffness, swelling, pain, and fatigue. Due to the limited number of participants, evaluation of benefit will be preliminary, so any potential benefit will need to be further evaluated in subsequent studies.

In Period 2, chronic splenic nerve stimulation is continued and provides an opportunity for participants to benefit from Stim ON with or without other cs, ts or bDMARDs and optimising stimulation parameters in the context of a clinical study with structured safety monitoring and close follow up.

Although there may be no direct benefits to the study participants, study participation will contribute to new knowledge of the effects of splenic nerve stimulation on chronic inflammatory diseases.

The risks due to stimulation and lead insertion have been characterised from preclinical studies, from multiple human cadaveric studies, and from an acute-intraoperative trial in participants undergoing planned esophagectomy. Data available until now have enabled us to quantify and mitigate potential adverse effects as indicated in Table 1.

Table 1 Risks of clinical significance derived from risks rated Notable or High in the Galvani risk management process

Potential Risk	Description of risk and rationale/data	Mitigation strategy
Risk Related to Implantation Procedure		
Risk of bleeding and damage to the splenic artery neurovascular bundle during dissection of the splenic artery and associated NVB in preparation for cuff application.	Bleeding may occur during dissection of the artery and preparing the arterial segment for application of the neurovascular bundle, Additionally, during dissection, retraction and manipulation, of the splenic artery NVB, the splenic nerve may be damaged. This may be temporary or permanent. In the case the splenic artery is permanently damaged, blood supply to the spleen may be altered. The long-term impact of splenic nerve denervation is not known but there are no reported complications due to denervation following pancreatic surgery. The long-term impact of splenic immune function, of loss of blood flow through the main splenic artery, has not been precisely characterized.	1. Selection of participants with extra-pancreatic loop based on cross sectional imaging (i.e., based on CTA or MRA) 2. Selection of participants with arterial loop that is accessible using minimally invasive techniques based on cross sectional imaging 3. Selection of study sites for implantation that routinely care for complex patients and which provide 24/7 availability of medical, surgical and radiologic specialties. While this may not reduce the incidence of a specific adverse event, it would be expected to facilitate early diagnosis and management which would reduce the severity of any patient effect. 4. Selection of surgeons who are trained and have an active practice involving foregut surgery or hepatobiliary surgery. 5. Training of surgeons 6. Damage caused by cuff mitigated by design & verified by benchtop and large animal testing
Risk of bleeding and damage to the splenic artery neurovascular bundle during dissection of the splenic artery and associated NVB in preparation for cuff application.	Bleeding from manipulation of retroperitoneal tissues.	● 1, 2, 4 & 5
Risk of bleeding and damage to the splenic artery neurovascular bundle during dissection of the splenic artery and associated NVB in preparation for cuff	Acute sequelae from splenic artery dissection: ● Acute disruption ● Acute thrombosis	● 1, 2, 4 & 5 ● 1, 2, 3, 4 & 5

application.		
Risk of bleeding and damage to the splenic artery neurovascular bundle during dissection of the splenic artery and associated NVB in preparation for cuff application.	Chronic sequelae from arterial dissection (pseudoaneurysm formation and arterial stenosis with or without arterial thrombosis).	1, 2, 3, 4 & 5. There are collateral sources of blood flow to the spleen so that in other clinical situations the loss of the main splenic artery does not result in the need for splenectomy.
Risk of bleeding and damage to the splenic artery neurovascular bundle during dissection of the splenic artery and associated NVB in preparation for cuff application.	Injury to the splenic nerve plexus with loss of ability to deliver therapy.	1, 2, 4, 5 and 6
Risk of bleeding and damage to the splenic artery neurovascular bundle during dissection of the splenic artery and associated NVB in preparation for cuff application.	Injury to the pancreas with possible: - Pancreatitis - Leakage of pancreatic fluid (Pseudocyst or pancreatic fistula formation)	1, 2, 3, 4 & 5 1, 2, 3, 4 & 5
Injury caused by the implant or explant surgery	The surgical procedure, used to place the system, may cause bleeding or injury to other intra-abdominal structures. While the risk of occurrence is expected to be low mitigation strategies have been implemented to reduce injury to the: liver, stomach, colon, small intestine, spleen and abdominal wall.	1, 2, 3, 4 & 5 - System performance and study participant health status will be monitored during regular follow-up visits to identify any effects of altered organ function
Skin erosion associated with subcutaneous placement of the IPG.	When an IPG is implanted in the subcutaneous space there is a risk of skin erosion which may necessitate removal of the system. Erosion is more likely to occur in the event of poor wound healing.	- Selection criteria including a 2.5 cm abdominal wall thickness limit as assessed by imaging studies have been implemented in this protocol to ensure that participants will be good candidates for placement of the IPG in the falciform ligament pocket thereby minimizing the probability of subcutaneous placement - The surgical procedure used to implant the IPG has been

		designed to reduce the risk of poor wound healing • The Galvani System IPG has been designed to minimize its size and as such is much smaller than those of other devices typically placed in the subcutaneous pocket, which is expected to further reduce erosion risk
Surgical site infections	• Superficial surgical site infection (skin and subcutaneous tissues) • Deep space infection	• 1, 2, 4 & 5. The system design and implant procedure isolate the system from potential superficial surgical site infections, in an effort to reduce the chance of the system becoming infected due to a superficial surgical site infection. • 1, 2, 4 & 5
General surgical side effects	The perioperative effects of general anesthesia and the systemic response to the physiologic stress of surgery and anesthesia have been characterized for patients with rheumatoid arthritis. These include pulmonary disease, coronary artery disease, hyper-coagulability and cervical spine subluxation.	• Performing preoperative screening with a history and physical examination, ECG, and appropriate physiologic testing, radiographic imaging and laboratory testing as determined by their rheumatologist or primary physician at entry to the study and surgeon or anesthesiologist during the preoperative evaluation • Intraoperative monitoring and management by the anesthesia team • Postoperative management and follow-up will be conducted according to the clinical judgement of the anesthesia team, surgeon and rheumatologist.
Potential Risks Associated with Active Stimulation		
Off target stimulation	Sequelae of off target stimulation from an intact system related to stimulation of the splenic plexus: • Sensation that therapy is being delivered. • Nociception during therapy delivery. • Altered pancreatic function:	• Cessation of therapy delivery • Changing the intensity of therapy delivered by reprogramming the system • Changing the time of day therapy is delivered • Monitor for altered GI function • Monitor perioperative glucose levels

	○ Exocrine ○ Endocrine ● Elevated blood pressure and/or other cardiovascular sequelae.	
Off target stimulation	Unwanted stimulation effects. This risk is attributed to two device failure modes: ● A lead fails in such a way as to generate unintended target site stimulation, ● An IPG which unintentionally leaks stimulation current onto the device can cause unwanted stimulation. Elevated blood pressure and/or cardiovascular sequelae are possible.	● Leads and IPGs are rigorously tested as part of the Design Phase activity including margin to failure, burn in, and fatigue testing ● Validated and monitored manufacturing processes will be used ● Stimulation output power has several levels of control and can be disabled in several ways ● Resolution of device failures may include lead replacement (during implantation) and/or IPG replacement.
Ineffective therapy	Discontinued Treatment due to Ineffective Therapy, not device related. - This risk is attributed to lack of therapy benefit or lack of therapy acceptance, due to factors which may include undesired collateral effects of stimulation (e.g., elevated blood pressure, pain). This risk is a known complication in the space of Neurostimulation.	● Careful monitoring of participant by treating physician ● Stimulation parameters can be adapted within the acceptance range for the patient ● Stimulation output power has several levels of control and can be disabled in several ways ● Cessation of therapy ● Additional monitoring during and following ramp-up visits, and/or enhanced design and adjusted surgical procedures based on early clinical results.
Ineffective therapy	Discontinued Treatment due to Ineffective Therapy, device related. The risk is attributed to system failure due to failure of either the IPG or the lead, resulting in a diminishment or loss of therapy.	● System failures related to the IPG will be mitigated by careful monitoring of the patient and IPG replacement ● System failures related to the implanted lead will result in therapy being discontinued.
Serious infection Malignancy	Splenic nerve stimulation acts via modulation of multiple inflammatory pathways including the cytokines IL-1β, IL-6 and TNF-α. Therefore, there is a theoretical risk that splenic nerve stimulation may	● Exclusion criteria for participants with current or recurrent infection and/or malignancy have been incorporated into this protocol (please see Section 5.2).

	be associated with adverse events manifested by suppression of these pathways, including immunosuppression class effects. However, available pre-clinical data suggest that splenic nerve stimulation exerts immunomodulatory rather than immunosuppressive effects and therefore, is less likely than marketed products (i.e., bDMARDs) to cause such adverse events (see Section 2.2.2).	- Participants will also be actively monitored for the development of adverse events. - Investigators are advised to bring participants up to date on their vaccinations no later than 30 days prior to randomization (Day 1) and to avoid live vaccination during treatment with active stimulation.
Potential Risks Related to the Galvani System		
Loss of therapy	There is a risk that the implanted device will use more energy than normal resulting in the loss of therapy. This may happen periodically while the IPG is implanted. If this happens the participant/patient can identify it in one of three (3) ways: they may see the battery levels on their remote drop quicker than normal, they may notice that they are not receiving scheduled therapy, or they may not be able to connect the remote to the device. In order to restore therapy, the patient will have to charge the IPG to a normal level which will temporarily require more charging time than usual.	To reduce the likelihood that a defective device is implanted, the following mitigation has been implemented: - IPG longitudinal screening (minimum 30-days) has been implemented before releasing IPG kits for implantation. This could reduce the likelihood of implantation of a defective device to below 1%. Additional measure to minimize end effects: - Two (2) chargers may be provided to the patient to facilitate the charging of a depleted IPG after elevated current events.
Cardiovascular effect Arrhythmia	This risk is attributed to leakage currents on a damaged lead with an insulation breach which may couple stimulation energy to heart tissue due to a close-proximity implant location.	- Lead design and reliability tested against insulation breach - Labeling cautions introduced in System Implant Manual to direct the correct handling of lead with surgical tools - Device check prior to activation 12-lead ECG monitoring at stimulation ramp-up sessions
Cardiovascular effect Arrhythmia	This risk is attributed to leakage currents on the IPG which may couple stimulation energy to heart tissue due to a	IPG and lead connector performance tested against leakage currents

	close-proximity implant location	• Lead connector dimensions measured for each manufactured lead • Labeling cautions introduced in System Implant Manual on full insertion of lead connector into IPG header • Device check prior to activation • 12-lead ECG monitoring at stimulation ramp-up sessions
Bleeding	This risk is attributed to the Galvani Trocar Surgical Tool, causing potentially catastrophic vascular injury during intended use.	• Blade mechanism and valve leakage tested inline for each manufactured trocar • Surgeons trained on trocar use
Bleeding	This risk is attributed to the exposure of the lead electrode edge during Cuff deployment/removal, Lead anchoring, or Deployment tab removal, causing potentially catastrophic vascular injury during intended use.	• Individual leads go through inspection for sharp edges and electrode protrusion during manufacturing • Surgeons trained on safe lead implantation and tab removal.
Pseudoaneurysm	This risk is attributed to the distal end of the Lead (i.e., cuff) causing unrecognized arterial damage that could eventually result in catastrophic vascular injury.	• Long term follow-up imaging per protocol • Additional follow-up imaging on suspected diagnosis of pseudoaneurysm
Organ damage	This risk is attributed to a Trocar which malfunctions during blade deployment.	• Blade mechanism and valve leakage tested inline for each manufactured trocar. Surgeons trained on trocar use.
Cardiovascular effect	This risk is attributed to an IPG interfering (radiated or conducted) with a patient's Implantable Cardiac Rhythm Management device: associated clinical sequelae/arrhythmia are possible.	• Patients with Implantable Cardiac Rhythm Management devices excluded from the study
Cardiovascular effect	This risk is attributed to a Charger interfering (radiated or conducted) with a patient's Implantable Cardiac Rhythm Management device:	• Patients with Implantable Cardiac Rhythm Management devices excluded from the study

	associated clinical sequelae/arrhythmia are possible.	
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The anticipated adverse effects that these risks could cause are documented in Appendix I.

4.6. DMARD BACKGROUND AND RESCUE OPTIONS

All participants will continue on a standard dose(s) conventional synthetic DMARD(s) including MTX, leflunomide, hydrochloroquine or sulfasalazine, or a stable combination of those. In addition, prednisolone or equivalent is allowed at a dose 5 mg/day. The participant's level of disease will be assessed regularly throughout the study (as shown in Section 7.1).

Intra-articular injection of a corticosteroid is allowed as rescue therapy in maximal three joints in case of severe flares as judged by the treating physician. These joints should be counted as swollen or tender as presented on the day of injection of the particular joint for the rest of the study. Rescue with DMARDs / biologics or JAKI's is not allowed in Period 1 of the study, unless the participant experiences an excessive disease flare that, in the investigator's opinion, warrants a change in therapy.

In Period 2, the RA standard of care medication may be adapted at the discretion of the Investigator or delegate.

4.7. END OF STUDY DEFINITION

The end of the study is defined as completion of the Month 60 visit in Period 2 of the last participant in the study or, in case any participant at this point in time has ongoing ADEs or SADEs, until these events have resolved, stabilised, or been otherwise explained.

Continuing stimulation is allowed when market approval is received for the Galvani system at the End of Study Visit. Galvani may elect to extend follow-up of participants enrolled in Period 2 after the study ends if market approval is not reached (see section 6.7) allowing participants to continue stimulating. If participants do not want to proceed with stimulation or withdraw early and refuse any further participation in the study and the device is not removed, then the device should be turned off and placed in hibernation mode by the PI or FCE and all accessories should be returned to the Sponsor, and if possible, the procedures for the Early Withdrawal (EW) Visit should still be performed (see section 7.1, Table 3 and Table 7).

If patients want to have their device explanted either during or at the end of the study see section 7.8.5.3.

5. STUDY POPULATION

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or participant safety. Therefore, adherence to the criteria is essential.

Note that “Inadequate Response” to prior treatment in this population is defined as: In the opinion of the investigator, after at least 3 months of treatment the participant experienced insufficient efficacy or loss of response as defined per local guidelines that would trigger a change of treatment, or the participant discontinued treatment due to intolerability or toxicity irrespective of treatment duration.

5.1. INCLUSION CRITERIA

Participants must meet all following inclusion criteria in order to be eligible for enrollment in this study:

- Adult-onset RA of at least six months duration as defined by the 2010 ACR/EULAR classification criteria.
- Male or female participants, 22-75 years of age inclusive at time of signing the IC.
- For Female Participants Only: A female participant is eligible to participate if she is not pregnant or breastfeeding or planning on becoming pregnant in the future, and one of the following conditions applies:
 - Is a woman of non-childbearing potential (WONCBP) as defined in Appendix I Fertility Definitions, Contraceptive Guidance and Collection of Pregnancy Information; OR,
 - Is a woman of childbearing potential (WOCBP) and using an acceptable contraceptive method as described in Appendix I during the study intervention period and thereafter while the device is implanted.
 - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 4 weeks before the implantation date, see Section 7.5.5 Laboratory Safety assessments.
 - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Participants must have active disease as defined by:
 - At least 3 swollen joints
 - A DAS-CRP>3.2 and/or CRP >15 mg/L.
- The participant must have an IR to at least two biologic DMARD and/or a JAKi. Participants must have an appropriate washout as described below for previously used biological DMARDs or JAKi.

Biologic agents:

 - Anakinra, etanercept; adalimumab; Infliximab; certolizumab pegol, golimumab, abatacept, tocilizumab, or other IL-6 blocking agents; tofacitinib, baricitinib or other JAKI's must be discontinued 2 weeks before surgery.
 - Rituximab, or other selective B lymphocyte depleting agents 6 month prior to Day 1.
 - Any prior investigational treatment must be discontinued for 2 weeks or 2 half-lives, whichever is longer, prior to surgery.

5.2. EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

- Inability to provide IC.
- In the opinion of the PI significant psychiatric disease or substance abuse.
- History of unilateral or bilateral vagotomy.
- Evidence of active or latent (unless previously treated) tuberculosis
- Known infection with human immunodeficiency virus (HIV) or positive test at screening
- Current acute or chronic hepatitis B and/or C, or previous hepatitis B (Hep B anti-core Ab+)
- Currently implanted electrically active medical devices (e.g., cardiac pacemakers, automatic implantable cardioverter-defibrillators).
- Any investigational small molecule drug or biological within 2 weeks or 2 half-lives whichever is longer, before surgery.
- Uncontrolled other inflammatory diseases
- Current/recurrent infections that in the opinion of the PI risk>benefit.
- History of cancer within the past 5 years, except non-malignant skin cancer.
- Previous splenectomy.
- Participants with an AWT, epidermis to posterior rectus sheath, greater than 2.5 cm based on ultrasound assessment or CT-scan.
- Chronic use of morphine or oxycodone.

Exclusion criteria related to the surgery and implant procedure:

- Type IV hiatal hernia and any hiatal hernia that produces a significant distortion of the local anatomy, especially the pancreas and/or splenic artery.
- Gastric resection/mobilisation surgery with surgical access of the lesser sac.
- Celiac axis, aneurysms or anatomy associated with congenital anomalies of the origin of the splenic artery.
- Splenic artery anatomical variants - splenic artery which is entirely within the substance of the pancreas or the presence of the splenic artery aneurysms or pseudoaneurysms.
- Direct contact between the splenic artery and the splenic vein, in the area identified for cuff placement.
- Participants who do not have a demonstrable clear plane between the pancreas and the splenic artery, at the interface site, in the preoperative computed tomography (CT) angiogram.
- Findings of cirrhosis or portal hypertension.
- Documented history of pancreatitis with significant peripancreatic inflammation (CT evidence of necrosis, pseudocyst formation or significant retroperitoneal calcification).
- Pancreatic abnormalities/mass/cyst/pseudocyst/lesions.
- Prior pancreatic resection.
- Splenic pathology (e.g. splenic abscess, malignancy, prior embolization or vascular anomalies that distort local anatomy).

- Any condition per the investigator's clinical judgment that qualifies the participant not fit for surgery.
- Body Mass Index (BMI) ≥ 33 .
- Splenic artery diameter as accessed by CT angiography <3.0 mm or >7.4 mm.

5.3. SCREENING/BASELINE FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but do not meet all of the inclusion criteria and / or meet one or more exclusion criteria. A minimal set of screen failure information will be collected during the 28 days screening period including demography, eligibility criteria, screen failure details, height, weight, BMI, and any serious adverse events (SAEs) considered related to participation in the study and if available, AWT and splenic artery lumen diameter.

5.4. RE-SCREENING

If a participant has not met all the criteria within the 42-day screening period, re-screening is required. Participants are only allowed to be re-screened once; the entire screening process must be repeated, except for the ultrasound and CT scan and the participant will be assigned a new unique participant identification number.

If a participant fails any of the laboratory criteria, the test may be repeated once within the screening period. If the participant fails the laboratory criteria for a second time, they will be considered a screen failure.

If a blood sample has to be redrawn due to sample handling problems, breakage or sample integrity, this is not considered re-screening.

5.5. PERMITTED AND PROHIBITED THERAPIES

Permitted and prohibited therapies are described below. Please see Manual of Procedures for further details.

5.5.1. PERMITTED THERAPIES PERIOD 1

Permitted therapies include:

- Glucocorticoids up to a prednisone equivalent dose of ≤ 5 mg/day are allowed.
- New topical steroids and other topical immunosuppressive agents (e.g., eye drops, creams) are permitted.
- Any intramuscular, intravenous or intra-articular corticosteroids 4 weeks before Day 1 are allowed.
- Non-steroidal anti-inflammatory drugs (NSAIDs) as needed.
- Intra-articular injection of a corticosteroid is allowed as rescue therapy in a maximum of three joints if a participant experience a severe flare as judged by the treating physician.

- Comfort measures including paracetamol, heating pads or ice packs, exercise, rest, yoga are permitted.
- Strong and weak Opioids for pain. Opiates must not be taken 24 hrs prior to RA disease activity assessment visits.
- MRI (Magnetic Resonance Imaging) may be performed following assessment for patient eligibility using Galvani's MRI Eligibility Form, and consultation with the latest Instructions for Use (IFU) guidelines. MRI procedures should be performed using ONLY 1.5T and 3T horizontal closed bore MRI systems.

5.5.2 PERMITTED THERAPIES PERIOD 2

The following concomitant medications are allowed for treatment of RA during the course of the Period 2:

- All csDMARDs approved for use for the patient
- All bDMARDs and tsDMARDs approved for use for the patient including, but not limited to, where relevant, infliximab, adalimumab, tocilizumab, and baricitinib.
- All other approved medications including glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), and paracetamol
- Heating pads or ice packs, exercise, rest, and yoga
- Strong and weak opioids for pain.
- MRI (Magnetic Resonance Imaging) may be performed following assessment for patient eligibility using Galvani's MRI Eligibility Form, and consultation with the latest Instructions for Use (IFU) guidelines. MRI procedures should be performed using ONLY 1.5T and 3T horizontal closed bore MRI systems.

5.5.3. PROHIBITED THERAPIES INCLUDE:

1. Diathermy, bipolar electrocautery (and other Prohibited interventions from the Implant/Clinician manual) are prohibited from the time of implantation onwards.
2. In Period 1 biologic or targeted synthetic DMARD with the exception that if to the investigator's judgement the participant is experiencing a systemic flare which needs treatment with a b/ts DMARD these can be subscribed.
3. Investigational treatments throughout the study period.
4. Use of external electrical stimulation devices
5. Placement of other electrically active implantable medical devices (e.g., cardiac pacemakers, automatic implantable cardioverter-defibrillators)
6. Therapeutic radiation
7. Extra-corporeal shock wave lithotripsy

5.6. PARTICIPANT WITHDRAWAL/DISCONTINUATION CRITERIA

5.6.1. PARTICIPANT WITHDRAWAL

Participants may withdraw consent at any time for any reason or may be discontinued from the trial at the discretion of the investigator(s) for safety, behavioral or compliance reasons.

If a participant withdraws for any reason during Period 1 of the trial, the participant will be asked to attend an early withdrawal visit (follow the procedures as Day 84 Period 1) and will be asked to attend the remaining visits in this study to monitor the participant for safety. After a participant has completed Period 1 or withdrawn early, they will proceed to the (LTFU) Period 2 (see Section 6.4). If a participant withdraws for any reason during Period 2 they must complete assessments of the Month 60 visit, at their withdrawal visit. If the participant cannot or will not participate in the efficacy evaluation until week 12 and Period 2, either the device can be in active mode if the participant experiences some benefit of the stimulation and will consent to participate in safety follow-up visits, or the device will be turned-off and the participant will need to return the accessories (PR and IPG charger) to the sponsor. The rationale is to continue monitoring safety in participants implanted with the Galvani System and to offer the participant rescue therapy if deemed appropriate.

The reason for discontinuation will be stated in the electronic case report form (e-CRF). If the reason for removal of a participant from the study is an adverse event, or an abnormal laboratory test result, this specific event or test will be recorded in the e-CRF.

If a participant withdraws, the data including results from samples analysed to the point of withdrawal remain part of the study. He/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Symptoms or signs that result in early withdrawal from the study will require documentation from the investigator attesting to the inadequacy of joint injections and / or requirement for rescue treatment.

In case a participant is deceased during the clinical trial the death e-CRF (date, cause, relatedness) will be completed. It is recommended to explant the device and return to Galvani, as certain end-of-life rituals (cremation) may be unsafe with device.

5.6.2. LOST TO FOLLOW-UP

The investigator will make every effort to regain contact with a lost participant. Where possible 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods will be used. These contact attempts will be documented in the participants medical record or study file.

Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

Note that the device will automatically disable the therapy schedule and any programmed stimulations will cease after the sunset timer has passed without a follow up visit. The sunset timer is automatically reset at every visit.

5.6.3. REPLACEMENT STRATEGY

If a participant withdraws from the trial before implantation, or because implantation is abandoned due to previously unrecognised surgical exclusion, a replacement participant may be enrolled and undergo implant attempt to meet the trial objective.

5.6.4. FOLLOW-UP OF PARTICIPANTS WITH AN ADVERSE DEVICE EFFECT

Adverse Device Effects (ADEs) and Serious Adverse Device Effects (SADEs) will be evaluated by the DSMB on a regular basis. In case an ADE results in a temporary hold of the scheduled therapy (e.g., if a software upgrade is needed), the participant can continue in the study if the halt of scheduled therapy is <15 days of the 84 days treatment in Period 1 and not more than 7 days in a row. If the period is >15 days or more than 7 days in a row in Period 1 the participant will be followed in the study for safety only and after Day 84 will proceed to Period 2. The participant will be able to restart therapy as soon as the issue is resolved, in consultation with the investigator.

5.7 CLINICAL STOPPING CRITERIA

5.7.1 IMPLANTATION PROCEDURE HOLD & STUDY SUSPENSION OR EARLY TERMINATION

During the conduct of this study, implantation of participants with the Galvani system will be put on hold, pending full review, should clinical events occur as described below. These events have been identified reviewing potential adverse events with a possibility of a direct procedural related cause. While efforts have been made to mitigate these risks, should these adverse events be observed it has been determined that implantation of the Galvani system will be put on hold until the results of a full review of the events has been undertaken by the DSMB. The results of this analysis will be reviewed with the appropriate regulatory bodies and a determination will be made if it is safe to continue implanting the system in participants. In addition, provisions relating to the premature termination of the research study and circumscribing the conditions under which termination may occur, insofar as termination occurs after one or more research subjects have undergone treatments or have had conduct requirements imposed on them, are set out in Section 12.2 of the Clinical Trial Agreement.

The clinical events that would trigger a hold on a study include:

1. Acute rupture of the splenic artery, noted intraoperatively in one participant
2. Delayed rupture of the splenic artery, or the development of a pseudoaneurysm in the area of arterial dissection and cuff placement, seen postoperatively in one participant
3. Intraoperative bleeding requiring conversion from a laparoscopic to an open surgical procedure to control the bleeding in one participant
4. Procedure related trauma to the spleen that necessitates splenectomy or splenorrhaphy during the index procedure in one participant
5. Delayed rupture of the spleen in one participant
6. The development of acute pancreatitis in two participants
7. The development of pancreatic pseudocysts or pancreatic fistula requiring intervention in two participants

The sponsor may suspend or prematurely terminate either a clinical investigation in an individual investigation site or the entire clinical investigation for significant and documented reasons (ISO14155:2001). The sponsor may terminate the investigation if the Galvani System is associated with a serious adverse device effect(s), observed in this or other studies, that may impact its safe use in this study; if recommended by the DSMB upon assessment of individual or accumulating safety data; or if unforeseeable circumstances prevent execution of this study as specified in this protocol.

5.7.2. INDIVIDUAL PARTICIPANT INVESTIGATIONAL PRODUCT STOPPING CRITERIA

Splenic neurovascular stimulation is an immune modulating therapy and as such may adversely impact the disease course of participants who develop serious infections (including, for example, opportunistic infections) and/or malignancies (see Section 4.5, table 1). Participants should be monitored closely for the development of such events. In the event a participant develops a serious infection (i.e.: infection reported as an SAE) or malignancy, investigational therapy (stimulation) should be stopped and should not be resumed until adequate resolution of the event. The Galvani medical monitor should be promptly (within 24 hours) notified of such occurrences

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), or medical device(s) intended to be administered to a study participant according to the study protocol. In Section 6.1 an overview of all study procedures and study visits is given.

6.1. STUDY SCHEDULE

Table 2 Overview of the study visits and procedures at each visit in Period 1

Visit	Procedures
Day -70-29	• Pre-screen & Identify potential participant • IC signed (participant enrolled)
Rheumatologist	Screening qualification • Eligibility criteria • Ultrasound to evaluate AWT • Demographics and medical history • Physical exam • Current and previous medication • PROs/Questionnaires/Disease Assessments • Safety evaluation
Surgeon	Additional, pre-Implant screening • Eligibility for implant • Surgical consultation • CT-angiography scan • Pre-Op clearance • SAEs
Day -28	Surgery (Implant)

Visit	Procedures
	• Implant • Intraoperative stimulation and measurement of cardiovascular response • Abdominal X-ray to confirm baseline position of cuff • Stim OFF • Concomitant Medication • (S)AEs and (S)ADEs • Overnight hospital stay after implant
Day -27	Release from hospital (Surgeon) • Post-Op Check • Concomitant Medication • (S)AEs and (S)ADEs
Day -18 (PostOp day 10)	Post-op Check (Surgeon) • Wound healing check and post-op clearance by surgeon • Vital Signs • Concomitant Medication • (S)AEs and (S)ADEs • IPG log data collected and analysed (FCE)
Day -7	Pre-stimulation check (Rheumatologist office/FCE) • IPG log data collected and analysed • Charging IPG • PR and charger provided with training and manual • Concomitant Medication • (S)AEs and (S)ADEs
Day 1	Baseline evaluations • PROs/Questionnaires/Disease Assessments • Biomarkers • Safety Evaluations Device ON • IPG log data collected and analysed • Dose escalation as per protocol • Stimulate 5 min at pre-defined target or 1mA below MTD • Device programmed for simulation • Biomarkers at 4 hours after first stimulation
Day 4	• Dose escalation as per protocol if target dose has not been reached • Adjust stimulation program • Safety Evaluations
Day 7	• Collect and retain samples for biomarker analysis • Dose escalation as per protocol if target dose has not been reached • Final dose set if target dose has been reached • Adjust stimulation program • Safety Evaluations
Day 14, 28	• Dose escalation per protocol if target dose has not been reached • Collect and retain samples for biomarker analysis • Adjust stimulation program (if needed) • PROs/Questionnaires/Disease Assessments

Visit	Procedures
	• Safety Evaluations
Day 42 and 56	• PROs/Questionnaires/Disease Assessments • Safety Evaluations • Collect blood for biomarker analysis (according to protocol) • Introduce night-time stimulation or increase number of stimulations during day-time to 12 if night stimulation is not tolerated and remission is not reached on Day 42 or Day 56 as defined in protocol. • If night-time stimulation is introduced and remission is not reached on Day 56, the number of stimulations will be increased to 12 times over 24 hours.
Day 21, 35, 49, 63, and 77	• Weekly phone calls in between the in-person visits to verify regular use of the charger, in addition to verifying participant safety, tolerability and functionality of the system
Day 70	• PROs/Questionnaires/Disease Assessments • Safety Evaluations • Collect blood for biomarker analysis
Day 84	• PROs/Questionnaires/ Disease Assessments • Safety Evaluations • Collect blood for biomarker analysis
Enrolment in long-term follow-up (Period 2) (for study visit details see Table 7)	

6.2. SURGICAL PROCEDURE

6.2.1 ANESTHESIA

Patients with RA not only experience the articular manifestations of their disease but also are at risk of experiencing a number of non-articular manifestations as well as the systemic effects of agents used to treat RA. These include but are not limited to an increased risk of cervical spine subluxation, as well as coronary, pulmonary and hematologic disorders. In light of this it is recommended that the team responsible for the perioperative management of the participant (Anesthesia, Rheumatology and Surgery) coordinate the participant's medical management to balance the risks of disease activity with the potential wound healing effects of agents used to control the participant's disease taking into account the minimal washout periods as mentioned in Section 5.1. Additionally, the anesthesia team should implement the perioperative management according to their institutional standard of care as it relates to airway management, DVT prophylaxis and perioperative risk of patients at risk of cardiac and pulmonary disease.

6.2.2 SURGICAL PROCEDURE

Surgical implantation of the Galvani system (lead and IPG) into the abdominal cavity is performed using a procedure that is based on established laparoscopic techniques. The lead and IPG are implanted into the participant's abdominal cavity through a laparoscopic procedure using surgical tools and accessories. A detailed description of the procedure can be found in the Galvani System

Implant Manual, a schematic presentation of the final system implant is given in Figure 6. The implant procedure will be supported by a Galvani field clinical engineer (FCE). A surgeon proctor will support the initial cases performed (Section 11.3.1). A laparoscopic video recording of the surgical implantation will be obtained and may be used to help train other surgeons in this trial or other trials. The implanted system will be tested intraoperatively to verify system functionality. Testing will include two stimulation episodes (one at lower and one at higher amplitude, as identified in Section 4.3.1) while monitoring intraoperative vital signs and lead impedances. The duration of each stimulation episode may be shortened if vital signs indicate cause for concern.

Following the surgical procedure, the study participant will be provided with a Patient Identity Document (ID) and instructions to facilitate recovery after implant. Participants will be instructed on the following points:

- Consult with their study physician if they notice any unusual discomfort possibly related to their new implant.
- Inform personal physicians that they have an implantable system.
- Carry their Patient ID at all times.
- That high-power electrical equipment may affect their implant.
- Consult the study physician if the following medical treatments are required: MRI imaging, surgery with electrocautery or RF ablation, implant of another active implantable medical device, or defibrillation.

6.3. PACKAGING/LABELLING/HANDLING/STORAGE/ACCOUNTABILITY

The implantable components will be supplied sterile and in double packaging. All labels will be in accordance with the Medicines & Healthcare products Regulatory Agency (MHRA) regulatory requirements. The investigator is responsible for study treatment, reconciliation and record maintenance. Further guidance and information are provided in the Manual of Procedures.

6.4 LONG-TERM FOLLOW-UP (PERIOD 2)

All participants who are implanted with the Galvani system, and who either complete Day 84, or who is stopping stimulation before Day 84 are followed in Period 1 for safety only (Section 5.6.1), will proceed to Period 2. In Period 2, participants receiving stimulation will be followed every month for 3 months, then every 3 months for the first 2 years, then every 6 months thereafter. Participants with the system in sham mode will not be followed-up for efficacy measurements (see Table 7 for detail). Participants with the system in hibernation mode will only be followed-up every 6 months for safety of the implant.

Period 2 will impose fewer restrictions on stimulation dosing and concomitant medications, thus allowing physicians to pursue patient-specific treatment regimen that may increase participant chances to achieve disease remission. During Period 2, participants may continue to receive stimulation (see Section 6.4.1), or suspend stimulation (see Section 6.4.2), or may add or remove cs, b, or ts DMARDS, in consultation with their physician.

Period 2 will monitor safety of participants for at least 5 years after implantation.

6.4.1 LONG-TERM FOLLOW-UP IN PARTICIPANTS WITH STIMULATION

Participants who continue to receive stimulation will continue in Period 2 at the time of the last Period 1 study visit. Participant's stimulation will be at the same dose that participants received at Day 84. The same assessments as those performed at the Day 84 visit, except the biomarker analysis, will be performed during the follow-up visits.

Participants will attend study visits every month for the first 3 months of Period 2, then every 3 months for the first 2 years (at 6, 9, 12, 15, 18, 21, and 24 months) and then every 6 months thereafter (at 30, 36, 42, 48, 54 and 60 months) after start of Period 2. An Interim Visit must be performed a maximum of 1 month after any change in device settings. Interim visits (recorded as unscheduled visits) may also be performed at any time at the principal investigator's discretion.

6.4.2. LONG-TERM FOLLOW-UP IN PARTICIPANTS WITHOUT STIMULATION

In participants who do not receive stimulation, the system will be switched OFF and all accessories returned. They will be followed for device related AEs every 6 months for 5 years, (at 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months) after start of Period 2.

Galvani does not recommend that study participants undergo a surgical procedure to remove the implanted system components upon study withdrawal, exit, or LTFU Period 2. However, Galvani will support system removal if medically indicated or requested by the study participant and investigator, after appropriate discussion between the investigator, surgeon, and participant.

More specific instruction on removal or adjustment of implanted components is contained in the Surgical Manual. Explanted system components must be returned to the Sponsor (see 7.8.5.3).

6.5. PLANNED DOSE ADJUSTMENTS PERIOD 2

At the discretion of and after discussion between the PI and the FCE, based on the level of the disease activity at the visit, stimulation parameters may be increased or decreased. Allowable ranges for new parameters will be described in the Manual of Procedures. If during the Period 2, an increase in dose is desired to improve the clinical response (and participant's experience of the therapy is favorable) the number of stimulation episodes per day can be increased to 12, and/or night time stimulation episodes can be introduced if the maximal number of stimulations was not reached and night-time stimulation not introduced in Period 1. In addition, the amplitude might be increased to a maximal 20 mA if disease remission is not reached, and participants had not reached 20 mA in Period 1. The procedure to increase amplitude is described in section 7.8.

6.6. SCHEDULE FOR ADJUSTMENT OF STIMULATION FREQUENCY AND MEDICATION IN PERIOD 2

Participants may follow the following care pathway, but the pathway is not obligatory. Additional options will be at the discretion of the PI and when needed in consultation with the FCE.

1. Participants who are in remission at Day 1 of Period 2 as defined by DAS28 -CRP ≤ 2.6 :
 - a. Background medication may be withdrawn upon consultation with the treating physician or
 - b. Continue the current stimulation and background medication regimen.

2. Participants who reached a >1.2 change in DAS28-CRP in GAL1039 (at week 12, Day 84, vs baseline in Period 1) but are not in remission as defined by $\text{DAS28-CRP} \leq 2.6$ may continue the current stimulation and medication regimen until Month 3 in Period 2 since reaching full remission may take 24 weeks. If remission is not achieved at Month 3 of Period 2, the following actions may be considered:
 - a. Adjust the number of stimulations delivered per day up to the daily maximum (12 stimulation doses in a 24-hour period).
 - b. Increase amplitude up to a max of 20 mA.
 - c. Add new cs, ts or bDMARD. It is anticipated that management of drugs will be adjusted in addition to the stimulation therapy.
 - d. Set to stimulation OFF, treat and adjust participants medication according to the standard of care treatments, and participants will be follow-up for safety. Participants must return their accessories.
3. In participants who are non-responders at Day 84 of Period 2 as defined by a <1.2 change in DAS28-CRP (Day 84 vs baseline), the following actions may be considered:
 - a. Prescribe new cs, ts or bDMARD medications in addition to the stimulation therapy.
 - b. Set the Galvani System to hibernation mode, treat with other standard of care treatments, and participants will be follow-up for safety only. Participants have to return their accessories.
 - c. Increase amplitude over subsequent visits up to a max of 20 mA if not reached yet.
4. If at some time during the 5-year follow-up period participants want to restart stimulation since they have a permanent implant, e.g., if they are partial responders to their new initiated cs, b or ts DMARD and they want to try to bring the disease activity further down by adding stimulation on top of the treatment, this will be an option after discussion with the PI, or delegate, and FCE. The procedure to re-start therapy is described in section 7.8.2 and Figure 7.

6.7. TREATMENT AFTER THE END OF THE STUDY

Galvani may elect to extend follow-up of participants enrolled in Period 2 after the study ends. The additional follow-up may be initiated to monitor long term safety of the treatment and the device, and to give participants who receive benefit from the treatment an option to continue stimulation. If participants want to stop stimulation at the last visit, the Galvani System will be set in hibernation mode and the participants must return their accessories. Galvani does not recommend that study participants undergo a surgical procedure to remove the implanted system components upon study withdrawal or study completion. Details on total removal of the system are provided in section 7.8.5.3.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed except for immediate safety concerns. Therefore, adherence to the study design requirements is essential and required for study conduct.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

This section outlines the procedures or assessments to be performed. The exact timing for each procedure or assessment is listed in Table 3, Table 4 ,Table 5, Table 6 and Table 7.

7.1. SCHEDULE OF ASSESSMENTS

Table 3 *Schedule of Assessments*

Assessment	Screen	Surgery, Recovery & Device Check				Treatment period									Final Period 1 study assessment/ EW
		Day													
	-70 to -29	-28 ⁵	-27	-18±2	-7±5	1	4±1	7±1	14±2	28±3	42±3	56±3	70±3	84±3	
Informed Consent	R														
Medical, Disease and Therapy History	R														
Demography	R														
Inclusion/ Exclusion Criteria	R/S														
Abdominal Ultrasound	R														
CT-Scan	S														
X-Ray		S ¹													
QuantiFERON-TB Gold test, HIV, Hepatitis B and C serology (see Table 8)	R														
Autoimmune Serology (see Table 8)	R														
Patient Reported Outcomes / Questionnaires / Disease Assessments															
Patient’s Assessment of Arthritis Pain ²	R					R ⁷			R	R	R	R	R	R	
Patient’s Global Assessment of Arthritis ²	R					R ⁷			R	R	R	R	R	R	

Assessment	Screen	Surgery, Recovery & Device Check				Treatment period								
														Final study assessment/ EW
		Day												
	-70 to -29	-28 ⁵	-27	-18±2	-7±5	1	4±1	7±1	14±2	28±3	42±3	56±3	70±3	84±3
Physician’s Global Assessment of Arthritis	R					R ⁷			R	R	R	R	R	R
HAQ-DI ²	R					R ⁷			R	R		R		R
RAID ²						R ⁷			R	R		R		R
Swollen (68) & Tender (66) Joint Count	R					R ⁷			R	R	R	R	R	R
SF-36 Patient’s Assessment (PCS&MCS) ²						R ⁷				R		R		R
Participant’s Assessment of the Galvani System									R	R		R		R
Clinician’s Assessment of the Galvani System										R				
Participant's Perception of Therapy and Sensation							R	R	R	R	R	R	R	R
Safety Evaluations														
Physical Exam Full	R					R ⁷								R
Vital signs	R			S		R ⁷	R	R	R	R	R	R	R	R
12 Lead ECG ³	R					R ⁷	R	R	R	R	R	R	R	R
Laboratory Safety Assessments (haematology, biochemistry)	R					R ⁷	R	R	R	R	R	R	R	R
Urine Pregnancy Test ⁴	R	S ¹⁰				R ⁷				R		R		R
Concomitant Medication	R	S	S	S	R	R ⁷	R	R	R	R	R	R	R	R
AEs / ADEs / Device Deficiencies		S	S	S	R	R ⁷	R	R	R	R	R	R	R	R
SAEs /SADEs	R/S	S	S	S	R	R ⁷	R	R	R	R	R	R	R	R

Assessment	Screen	Surgery, Recovery & Device Check				Treatment period									Final Period 1 study assessment/ EW
						Day									
	-70 to -29	-28 ⁵	-27	-18±2	-7±5	1	4±1	7±1	14±2	28±3	42±3	56±3	70±3	84±3	
PreOp Clearance / PostOp Check	S	S	S	S ⁶											
Device															
Device Check		S		S	R	R	R	R	R	R	R	R	R	R	
Dose Escalation						R	R ⁸	R ⁸	R ⁸	R ⁸					
Adapt numbers of stimulation episodes a day and/or add night-time stimulation ⁹											R	R			
Instruction on using PR and/or IPG charger					R	R									
Unscheduled visits		As required													

EW = Early Withdrawal, R = Rheumatologists (PIs) responsibility, S = Surgeons responsibility. Some responsibilities will be delegated e.g., device check, device deficiency, dose escalation, instructions on use of Galvani neuromodulation system to the FCE.

1. X-ray of abdomen
2. All patient reported outcomes assessments should be conducted before any other assessments at this clinic visit
3. Triplicate at screening, single at all other time points
4. For women with childbearing potential. Additional pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study
5. Day of surgery. See additional table for procedures to be performed during surgery (Table 6)
6. If participant is not cleared during the post-operative review, then another visit should be scheduled and the assessments as on Day -18 repeated
7. Assessment performed / sample taken prior to stimulation (baseline)
8. Dose escalation may continue at this visit if prior visits fail to increase stimulation to target amplitude
9. If participant does not reach the clinical improvement as defined in the protocol.
10. On the day of implantation or up to 3 days before.

Table 4 *Schedule of Assessments – site telephone calls*

Assessment	Period 1 Open Label Phase				
	Day (Relative to Period 1 Day 1)				
	21±3	35±3	49±3	63±3	77±3
Study Week (Relative to Day 1)	W3	W5	W7	W9	W11
Device and Safety Check Telephone Call	R	R	R	R	R

R = Rheumatologists' responsibility

Table 5 *Exploratory Biomarker Assessments*

Assessment	Screen	Surgery, Recovery & Device Check				Treatment period									Final Period 1 Study assessment / EW
		Day													
	-70 to -29	-28	-27	-18±2	-7±5	1	4±1	7±1	14±2	28±3	42±3	56±3	70±3	84±3 ⁴	
Biomarker Assessments															
TruCulture						R ^{1,2}		R ³	R ³					R	
Plasma (cytokines & resolvins)						R ^{1,2}		R ³		R ³				R	
Whole Blood (EDTA)						R ¹				R				R	
Whole Blood (sodium citrate)						R ¹				R				R	

1. Sample taken prior to stimulation (baseline)
2. Second sample taken 4hr ± 1hr after the start of the stimulation
3. Sample to be stored for any potential retrospective analysis if required
4. End of study or Early Exit Visit.

Table 6 *Overview of system evaluation after implantation, day of surgery*

Procedure	Day-28 Surgery				
	Post Cuff Placement (IPG outside the body)				
	Pre -Stimulation 5mA	Stimulation 5mA	Rest Period	Stimulation 10mA	Rest Period
Cuff Fit Assessment	S				
Impedance ¹	S		S		S
Systolic Blood pressure	S	S	S	S	S
Heart Rate	S	S	S	S	S

S = Surgeons responsibility. Some responsibilities will be delegated e.g., measurement of systolic blood pressure and heart rate to anesthetist, measurement of impedance to FCE

1. Additional impedance measurements may be taken by the FCE as required

Table 7 *Schedule of Assessments for Period 2*

Assessment	Study Visits																
Study Month (Month $\pm$ Weeks)	Day 1 Period 2 (Day of last visit Period 1)	1M $\pm 2W$ 7	2M $\pm 2W$ 7	3M $\pm 2W$ 7	6M $\pm 2W$	9M $\pm 2W^7$	12M $\pm 2W$	15M $\pm 2W^7$	18M $\pm 2W$	21M $\pm 2W^7$	24M $\pm 4W$	30M $\pm 4W$	36M $\pm 4W$	42M $\pm 4W$	48M $\pm 4W$	54M $\pm 4W$	60M $\pm 4W$ / EW
PROs/Questionnaires/Disease activity Assessments																	
Patient's Assessment of Arthritis Pain ¹	Assessments Last Visit in Period 1	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Patient's Global Assessment of Arthritis ¹		R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Physician's Global Assessment of Arthritis		R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
HAQ-DI ¹		R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
RAID		R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Swollen (66) & Tender (68) Joint Count		R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R

SF-36 Patient's Assessment ¹		R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Participant's Assessment of the Galvani System		R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Clinician's Assessment of the Galvani System							R										
Participant's Perception of Therapy and Sensation		R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Safety Evaluations ²																	
Physical Examination Full	Assessments Last Visit in Period 1	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Vital Signs		R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
12 Lead ECG*		R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Laboratory Safety Assessments (haematology, clinical chemistry)*		R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Urine Pregnancy Test ³	As required																
Duplex Ultrasound for the Assessment of Splenic Artery Pathology ⁴							R						R				R
CT-angiogram	R																
Disease-Related, SAE-related and any Immuno-modifying Concomitant Medication	Assessments Last Visit in Period 1	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Disease related AEs/ADEs* / Device Deficiency*		R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
SAEs / SADES*		R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Device Check including impedance		R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Device charging (check device out of hibernation mode, charge and put back in hibernation mode) ⁵	As required (minimal every 18 month from start of hibernation)																
Biomarker Assessments																	

Study Month (Month ± Weeks)	Day 1	1M ±2W 7	2M ±2W 7	3M ±2W 7	6M ±2W	9M ±2W ⁷	12M ±2W	15M ±2W ⁷	18M ±2W	21M ±2W ⁷	24M ±4W	30M ±4W	36M ±4W	42M ±4W	48M ±4W	54M ±4W	60M ±4W
Banked Plasma		R	R	R	R	R	R		R		R		R		R		R
Blood draw for biomarker analysis (e.g. whole blood for FACS analysis)	As required based on GAL1039 Period 1 findings																
Device																	
Dose Escalation (restart of stimulation)/ Adjustment ⁶	As required																
Unscheduled Visit	As required																

1. All PRO assessments should be conducted before any other assessments at a clinic visit
2. Participants in which the device is in hibernation mode are 'followed for safety' meaning only the assessments as detailed in the safety evaluations section of this table will be performed, except the assessments marked with an *.
3. For women with childbearing potential. If stimulation is to be turned ON during Period 2 then a negative pregnancy test will be required prior to stimulation. Additional pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's enrollment in the study.
4. If the Duplex Ultrasound is non-diagnostic, repeat imaging with trans-abdominal ultrasound technique within 2-3 weeks would be advised. For repeated indeterminate results a definitive study – using CT angiogram, endoscopic ultrasound or other technique(s) – should be undertaken in accordance with local practice guidelines
5. Only participants with the device in hibernation mode.
6. See Section 7.6 for safety monitoring procedures during dose escalation, which include heart rate, blood pressure, oxygen saturation and serial ECGs.
7. Visit not applicable for participants with device in hibernation i.e. not receiving stimulation.

7.2. PARTICIPANT RECRUITMENT

Potential study participants will be identified in the PI practice. Review of potential participants' medical files may be utilized to determine preliminary eligibility according to inclusion and exclusion criteria, by the treating team (prescreening). Once a potential participant is identified, the the first approach will be made by one of patient's routine clinical team and the study will be discussed, this can be the PI or authorized designee. No other recruitment strategies are planned.

7.3 INFORMED CONSENT, SCREENING AND BASELINE ASSESSMENTS

Informed consent will be obtained from the participant prior to initiation of any study procedures or study-specific data collection. Assessments may be performed over more than one day as necessary.

7.3.1. INFORMED CONSENT

If the patient is interested, the Principal Investigator (PI) or authorised designee will explain the research study to the participant including its purpose, procedures, potential risks; and explain their rights as a research participant. Participants will have the opportunity to carefully review the written consent form for a minimum of one week, but can take as long as needed, prior to agreeing to participate. In addition the potential participant will be able to ask questions prior to signing and should have the opportunity to discuss the study with their family, relatives, independent physician, or GP. Before consenting, participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. If a participant is implanted and then withdraws, the PI should explain the importance of enrolling in the long-term follow-up (Period 2) as the device will still be implanted and the sponsor has a duty of care to follow the participant for safety reasons.

The rights and welfare of the participants will be protected by emphasising to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The participant and PI or authorised designee will sign and date the IC document.

A copy of the IC document will be given to the participants for their records. The IC process will be documented in the study participant's medical record. A participant is considered enrolled from the signing of the IC.

Participants must be re-consented to the most current version of the IC during participation in the study.

This study will not be carried out in vulnerable populations that include emergency situations preventing IC as specified above, in juveniles or in participants incapable of making informed judgements.

7.3.2. INCLUSION AND EXCLUSION CRITERIA

It will be verified that all inclusion and no exclusion criteria are met (see Section 5.1 and 5.2). The participant will at least have two appointments in the hospital; first the participant will be screened by the rheumatologist, and thereafter the participant will be seen by the surgeon. The surgeon will

review a new or recent (within the last 6 months) CT scan. Other assessments that will be used in preparing the participant for surgery and in final clearance of the participant for surgery will include but not limited to laboratory assessment as well as ECG or other diagnostic studies obtained at the discretion of the participant's rheumatologist and surgeon and will be made in accordance with the local standard of care for perioperative management of patients. Note that any screening exams (such as imaging) may be arranged by either rheumatologist or surgeon investigator upon mutual agreement, the surgeon investigator is responsible for assessing screening results for meeting criteria for implant.

7.3.3. SCREENING AND BASELINE (DAY 1) ASSESSMENTS

- The following demographic parameters will be captured: year of birth, sex, ethnicity and race.
- Medical history, smoking history and current status, and RA disease duration and current medical conditions will be obtained by the investigator or qualified designee.
- Physical examination.
- Vital signs.
- 12-Lead ECG (triplicate at screening only).
- An ultrasound will be performed to assess that AWT is not greater than 2.5 cm (screening only). The ultrasound may be repeated (or CT scan performed) if the ultrasound assessment is indeterminant.
- If the ultrasound indicates the AWT is 2.5 cm or less (or the ultrasound results are indeterminant), then a CT scan will be performed using a contrast agent to visualise the arteries according to the standard procedure of the hospital (screening only).
- Blood samples for:
 - Haematology (screening and baseline).
 - Biochemistry (screening and baseline).
 - Autoimmune serology: RF and ACPA (i.e., anti-CCP antibodies) (screening, if no data from the last 5 years is available).
 - Biomarkers (baseline).
- Urine samples for:
 - Urine pregnancy test.
- Disease activity assessments (screening and baseline) (see Section 7.5)
 - Tender joint count (68 joints)
 - Swollen joint count (66 joints)
 - Patient's assessment of Arthritis Pain.
 - Patient's Global Assessment of Arthritis.
 - Assessor's Global Assessment of Arthritis.
 - HAQ-DI
 - RAID (baseline only)
- Patient-reported outcomes questionnaires (baseline) (see Section 7.5.12)
 - SF-36 PCS&MCS

7.4. INTRA-OPERATIVE AND POST-SURGICAL ASSESSMENTS

7.4.1. INTRA-OPERATIVE STIMULATION

After implant of the cuff, but before implant of the IPG and the participant still inflated, two test stimulations will be performed according to the schedule presented in Table 6. The effect of stimulation on electrical impedance, heart rate and blood pressure will be recorded. The surgeon's assessment of cuff fit on the splenic NVB will also be recorded. See the Manual of Procedures for further details.

7.4.2. X-RAY OF THE ABDOMEN

An X-ray will be taken immediate post-surgery to document the cuff's position relative to anatomic landmarks for future reference in potential troubleshooting.

7.4.3. POST-OPERATIVE CHECK

On postoperative day 10 (Day -18) the Surgeon will assess the participant's recovery from surgery including a wound check, vital signs, AE and ADE assessments and concomitant medication review. The device will be checked at this visit by the FCE.

Participants who are not sufficiently recovered will remain under Surgeon care and additional post-operative assessment visit(s) will be performed as required, repeating Day -18 assessments. Device checks by FCE are not required to be repeated.

When a participant is declared sufficiently recovered from surgery, they will be referred back to their Rheumatologist to continue Day -7.

7.5. EFFICACY ASSESSMENTS

Efficacy measures will be performed at the time points presented in Table 3 and table 7.

Efficacy assessments will include evaluation of all 68 joints for tenderness and 66 joints for swelling to be performed by an independent joint evaluator, visual analog scale (VAS) (global disease) for the participant and treating physician, health assessment questionnaire – disability index (HAQ-DI – physical function, which includes an item on pain severity in the past week), as well as other health outcome measures described in more detail in Sections 7.5.10, 7.5.11 and 7.5.12 and laboratory safety assessments (CRP). Based on these assessments, nACR, CDAI, SDAI, DAS28(CRP) and the EULAR response will be calculated.

7.5.1. JOINT ASSESSMENTS

The procedure for joint assessments can be found in the Manual of Procedures.

7.5.1.1. REPLACED OR FUSED JOINTS

Replaced or fused joints will not be included in joint evaluations. The reason for absence of the evaluations of those joints must be recorded.

7.5.1.2. JOINT EVALUATOR

One or more assessors, who have documented experience in performing joint assessments, will be designated to perform joint assessments. Preferably the same assessor will perform all joint assessment for the same participant throughout the trial. The PI must ensure that the joint assessor has documented experience and he/she is adhering to locally accepted and implemented standards. This also applies if the joint assessor is replaced during the trial.

7.5.2. PATIENT'S ASSESSMENT OF ARTHRITIS PAIN

Participants will assess the severity of their current arthritis pain using a 100-unit VAS by placing a mark on the scale between "0" (no pain) and "100" (most severe pain), which corresponds to the magnitude of their pain.

Further details of this assessment are provided in the Manual of Procedures.

7.5.3. PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS

Participants will complete a global assessment of disease activity using the patient global assessment (PtGA) item, a VAS with anchors "0" (very well) to "100" (very poor).

Further details of this assessment are provided in the Manual of Procedures.

7.5.4. ASSESSOR'S GLOBAL ASSESSMENT OF ARTHRITIS

Physicians or delegate will complete a global assessment of disease activity using the physician global assessment item (PhGA), a VAS with anchors "0" (none) to "100" (extremely active), respectively.

Further details of this assessment are provided in the Manual of Procedures.

7.5.5. DAS ASSESSMENTS

At the specified timepoints data is obtained from different measurements with differential weighting given to each component. The DAS28(CRP) will be calculated at each assessment timepoint.

The components of the DAS28(CRP) arthritis assessment include:

- Tender/Painful Joint Count (28).
- Swollen Joint Count (28).
- CRP level
- Patient's Global Assessment of Arthritis.

7.5.6. ACR ASSESSMENTS

The American College of Rheumatology's definition for calculating improvement in RA (ACR20) is calculated as a 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant. Similarly, ACR50 and 70 are calculated with the respective percent improvement. This efficacy measurement will be made at every study assessment timepoint.

The specific components of the ACR Assessments that will be used in this study are:

- Tender/Painful Joint count (68).
- Swollen Joint Count (66).
- Patient's Assessment of Arthritis Pain.
- Patient's Global Assessment of Arthritis.
- Physician's Global Assessment of Arthritis.
- CRP level.
- Health Assessment Questionnaire – Disability Index (HAQ-DI).

7.5.7. EULAR RESPONSE RATE

The EULAR modified response rate will be calculated based on the criteria in **Table 8**.

Table 8 *EULAR response criteria*

Response Table		Changes in DAS28 -CRP from Baseline		
		>1.2	≥ 0.6 – ≤ 1.2	<0.6
Current value DAS28-CRP	<3.2	good	moderate	poor
	≥ 3.2 – ≤ 5.1	moderate	moderate	poor
	>5.1	moderate	poor	poor

7.5.8. CDAI ASSESSMENTS

The CDAI is a composite index for assessing disease activity based on:

1. swollen joint count (of a possible 28).
2. tender joint count (of a possible 28).
3. patient's global assessment of disease activity (VAS).
4. physician's global assessment of disease activity (VAS).

7.5.9. SDAI ASSESSMENT

The SDAI is a numerical sum of five measures:

1. swollen joint count (of a possible 28).
2. tender joint count (of a possible 28).
3. patient's global assessment of disease activity (VAS).
4. physician's global assessment of of disease activity (VAS).
5. CRP (mg/dL)

7.5.10. HEALTH ASSESSMENT QUESTIONNAIRE – DISABILITY INDEX (HAQ-DI)

The functional status of the participant will be assessed by means of the Disability Index of the Stanford Health Assessment Questionnaire (HAQ-DI). This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks in eight functional areas: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities.

7.5.11. RHEUMATOID ARTHRITIS IMPACT OF DISEASE QUESTIONNAIRE - RAID

A RAID value will be calculated using the participant completed RAID questionnaire. Participants will score 7 questions from 0 to 10 and these values, which are weighted differently, are used to calculate an overall RAID value.

7.5.12. SHORT FORM (SF)-36 HEALTH SURVEY

Health-related quality of life (HRQL) will be assessed using the participant-completed Medical Outcomes Study Short-Form 36 (SF-36) which is a generic health survey that contains 36 questions covering eight domains of health. The SF-36 yields an eight-scale profile of functional health and well-being scores as well as physical and mental component health summary scores. The version 2, 1-week recall questionnaire will be used.

7.5.13. PARTICIPANT AND CLINICIAN'S ASSESSMENTS OF THE SYSTEM

A questionnaire will be provided to assess participants' experience with device usability and participants' perception of device therapy. The physician will be requested to complete a similar device usability questionnaire within a month of when the a first participant at their site 12 Month's in Period 2.

7.5.14. PARTICIPANT'S PERCEPTION OF THERAPY AND SENSATION

The participant will also be asked to complete two questionnaires; one relating to their perception of therapy and another to sensation at the visits depicted in the schedule of assessment Table 3.

7.6. SAFETY ASSESSMENTS

Planned time points for all safety assessments are listed in Table 3 and Table 7.

Participants will have systematic safety monitoring throughout the study. Additional time points for safety tests (such as vital signs, physical exams and laboratory safety assessments) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.6.1. PHYSICAL EXAMINATION

Physical examination by organ system will be performed using standard clinical techniques. Physical examination will be recorded as normal or abnormal, abnormalities must be specified. The physical examination will include an examination of general appearance, skin, neck (including thyroid gland),

eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and a basic evaluation of the nervous system. Any persisting abnormalities must be stated each time the examination is performed. Significant findings that are present at screening must be included in the relevant medical history/current medical conditions of the e-CRF. All other significant findings which meet the definition of an AE must be recorded in the Adverse Event e-CRF summary page. Height (m) and weight (kg) will also be measured using standard clinical equipment (shoes off, jacket or coat removed).

7.6.2. ELECTROCARDIOGRAM (ECG)

Where possible 12-lead ECG measurements should be recorded before vital sign measurements and blood draws. Participants should be in a quiet setting without distractions and rest in a supine position for at least 5 or 10 minutes before ECG collection. Triplicate 12-lead ECG measurements will be obtained at screening with single ECG measurements obtained thereafter as outlined in Table 3 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

At the screening visit where triplicate ECG are required, three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

7.6.3. VITAL SIGNS

Vital signs will be performed resting in semi recumbent position. Vital signs include heart rate, systolic and diastolic blood pressure, temperature and respiratory rate. A single set of values will be collected and recorded in the source documentation and e-CRF

7.6.4. LABORATORY SAFETY ASSESSMENTS AND URINE PREGNANCY TEST

Laboratory Safety Assessments and urine pregnancy tests (when required) will be performed by the local hospital laboratory as per local SOPs.

The investigator must review the laboratory report, document this review, and record any clinically relevant adverse changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.

The following analytes will be tested:

Table 9 *Laboratory Safety assessments*

Laboratory Assessments	Parameters			
Haematology	Platelet Count	RBC Indices: MCV MCH	<u>WBC Count with Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	RBC Count			
	Haemoglobin			
	Haematocrite			
	Erythrocyte Sedimentation Rate			
Clinical Chemistry		Potassium	Aspartate aminotransferase (AST)	Total bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)	Direct bilirubin
	Glucose (non-fasting)	Chloride	Alkaline phosphatase (AP)	Total Protein
	Albumin	Urea	C-reactive protein (CRP)	
Immunology (at screening) ¹	- Rheumatoid Factor (RF) - Anti-cyclic citrullinated peptide (anti-CCP)			
Urine Pregnancy Test	Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)²			
Other Screening Tests	- Follicle-stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only) - Serology [HIV antibody, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis C virus antibody], herpes zoster. - QuantiFERON-TB-Gold plus			

1. If historical value within last five years is not available.

2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB.

7.6.5. SERIOUS ADVERSE EVENTS

SAEs will be recorded from signing of IC through to the last follow-up visit of the study (Mont 60 Period 2) (see Section 10 for details).

7.6.6. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

AEs (including disease-related events (DREs)), ADEs, and device deficiencies will be recorded from Day -28 through to the Day 84 follow-up (see Section 10 for details).

From start of Period 2 to last follow up visit, only disease related AEs (including disease-related events (DREs)), ADEs, and device deficiencies (DDs) will be recorded (see Section 10 for details). Adverse Events that are neither serious nor device -related are required to be recorded during Period 2.

7.6.7. CONCOMITANT MEDICATIONS

A list of all concomitant medications will be elicited from the participant at timepoints indicated in Table 3 and entered from source documents to the e-CRF.

In Period 2, only concomitant medications related to treatment of rheumatoid arthritis will be elicited from the participant at timepoints indicated in Table 7.

7.6.8. DEVICE CHECK

At each visit indicated in Table 3 and Table 7, the overall integrity of the system and participant use of the device will be verified by a sponsor representative (FCE) with the use of the CP (Section 2.2.3). Upon CP connection to the IPG, the current programmed settings will be verified. System integrity will be verified by reviewing system impedances. Device log data will be interrogated and reviewed for the elements that follow.

- System errors
- Approximately appropriate number of stimulus doses delivered since last visit
- Lead integrity as indicated by system impedance is within acceptable ranges.
- Approximately appropriate number of charging sessions since last visit (participant compliance charging the IPG).
- IPG battery level will be checked.

The IPG log may be inspected in greater detail if any problems with the system are suggested by the above review or based on historical experience with the study participant.

The above assessments will be recorded on appropriate case report forms. Indication of participant non-compliance or difficulty using the system (e.g., lack of charging sessions, incidents turning off the system) will be reported to the study physician (or delegate) for further discussion or clarification with the study participant. Additional training or coaching on system use will be provided as appropriate.

The log data will be copied to an encrypted USB stick supplied by Galvani and uploaded to a secure data repository for later inspection or analysis.

7.7. STUDY SPECIFIC LABORATORY TESTS (EXPLORATORY BIOMARKERS)

These assays will be undertaken by the study investigators. The following blood samples will be taken at the time indicated in the schedule of assessments (Table 3, Table 5 and Table 7). Protocols established for each assay have been refined to use the minimal blood volumes possible to complete the studies. These analyses will be performed with the aim to define signatures of dysregulated

immune responses at baseline, signatures that predict treatment responses, and changes in signatures that occur during treatment.

7.7.1. PLASMA SAMPLES

Samples will be analysed for extended autoantibody serotyping (including RF and ACPA isotype usage and fine specificity), measurement of inflammatory mediators including, but not confined to, cytokines, chemokines and growth factors, as well as factors associated with resolution of inflammation (i.e., resolvins), cartilage and bone catabolism, and with metabolism.

7.7.2. WHOLE BLOOD

Multi-parametric flow cytometric analysis with flow cytometry will be undertaken on blood to evaluate distribution and phenotypes of cell subsets.

7.7.3. PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMCs)

Cells will be isolated and used either fresh or frozen for subsequent immune phenotyping by multi-parameter flow cytometric analysis and ex vivo stimulation assays.

These analyses will be performed at baseline and at study visits as indicated in Table 5. Details on the blood sample collection, processing, storage are provided in the Laboratory Manual. All samples may be retained for a maximum of 20 years after the last participant completes the study. Results of biomarker studies may be reported separately from the main clinical study report, and additional exploratory analyses may be performed to further characterise novel biomarkers.

7.7.4. BANKED SAMPLES

Plasma samples will be banked and may be used if exploratory analysis from this study or emerging evidence in the scientific literature suggest this analysis would support the objectives of this study or help to understand the results of this study. Excess supernatant from the whole blood assay may also be stored incase additional exploratory analysis is required.

Further research which is not related to this study, using banked plasma or supernatant will only be performed if separately agreed to in the IC.

7.8. DEVICE SETTINGS AND CHANGES

7.8.1. PARTICIPANT TRAINING

On the Day -7 visit. participants will be provided with an instruction manual, a PR, a Charger, and associated accessories (adhesive patches and/or charging belt). Participants will be trained to charge their IPG and use their PR and re-instructed on Day 1. During both these visits the participant will charge the IPG under guidance of the FCE. The participant can choose a charging interval that works for him or her, but will be encouraged to initially check battery level at least every other day and to charge as needed to maintain the IPG battery indicator (located on the Patient Remote) at 'High'. The

frequent visits starting on Day 1 will assist monitoring compliance. Details on IPG charging will be provided in the Galvani System Patient Manual. In addition, participants will be called weekly in between the in-person visits (called at around Days 21, 35, 49, 63, and 77) to verify use of the device and to provide additional coaching, as needed.

The PR can be used to check battery level before and after charging. Participants will also be trained to turn OFF their stimulation using both the Charger and the PR, in case they experience any unexpected discomfort that is believed to be associated with their implanted system. Participants will be instructed to call their study doctor immediately after they have turned OFF their system, and to schedule a programming visit. Other programming options and uses of the PR are presented in the instructions manual. Study participants will be instructed to bring their PR and Charger with them to each study follow-up visit.

7.8.2. DOSE ESCALATION VISITS

Initial post-implant stimulation and subsequent dose escalation will occur on Days 1, 4, 7 and 14 at a minimum. Additional dose escalation visits up to Day 28 may be scheduled to modify the rate of dose escalation based on individual participants' feedback and tolerability of dose escalations and in consultation with the sponsor. The study target dose for the participant to reach by the end of the final dose escalation visit will be 20 mA. In addition, dose escalation visits can happen throughout the Period 2. During this Period 2 participants can have their stimulation temporarily off (e.g., due to a COVID infection), or could restart stimulation as an adjunct therapy to their standard-of-care therapy.

During Dose Escalation Visits, stimulus amplitude adjustments will be performed by the sponsor representative (FCE) while an investigator (or delegated staff) monitors participant symptoms and vital signs. In addition, the Device Check will be performed as described in Section 7.6.8. During Dose Escalation Visits, stimulus amplitude will be increased from the previously programmed amplitude to a predefined target amplitude by the FCE. Stimulus amplitude increments may be suspended if the study participant expresses discomfort, and the final programmed amplitude may be lower than the predefined target amplitude (i.e., programmed to an amplitude below that which elicits discomfort).

Safety Monitoring procedures during ramp up visits will include the following measures:

- All participants will have vital signs and a 12-lead ECG taken at the outset of the visit.
- Prior to initiation of stimulation, participants will have an automatic blood pressure cuff and pulse oximeter applied.
- During ramp up stimulation, sensations and adverse events reported by the participant will be documented; site staff will also monitor the participant's heart rate, blood pressure (taken at approximately 5-minute intervals by the automatic blood pressure cuff) and oxygen saturation.
- In the event of any clinically significant abnormality in heart rate, blood pressure or oxygen saturation, or an AE report referable to cardiovascular symptoms, a repeat 12-lead ECG will be taken.
- A 12-lead ECG will also be taken immediately following the final stimulation given during the visit so that the Investigator may verify that there are no clinically significant ECG abnormalities prior to discharging the participant.

The visit on Day 1 will be the first programming visit to test stimulation since the implant procedure. Stimulation amplitude will be increased from 0 mA towards a predefined subthreshold target dose (5 mA) in increments of 1 mA (see Figure 7) in 5 ramp up stimulations. 0.5mA increments may be used in cases of low tolerability to stimulation. If during any visit, a stim level is reached at which the participant indicates discomfort, the stim level may be repeated or decreased (in steps of 1mA or 0.5mA), depending on the tolerance communicated by the participant or as indicated by the monitoring equipment. If the highest stim level that is tolerable for a visit is below the dose goal for that given Dose Escalation visit (for example, below 5 mA on Day 1), then the highest tolerable stim level is considered the Maximum Tolerable Dose (MTD). Further attempts will be made to increase the output during subsequent visits (up to Day 28) to the MTD or the Target dose of 20 mA. This because for several FDA-approved neurostimulation therapies, the threshold of tolerability can increase over time. Again, these subsequent visits can be also used to reduce a stim level reached in a previous visit if there is concern long term due to tolerability.

At the end of each visit, a final stimulation will be given at the last stim level achieved. Immediately following this, a 12-lead ECG will be taken. The system will then be programmed to automatically apply this stim level (or sham) at six times per day (every two waking hours).

At the end of the Day 1 visit, the study participant will be re-trained how to charge their IPG and use their PR. At Day 28, the final amplitude reached will be programmed and this stimulation dose (Target dose or MTD) will be given for at least 14 days unless an unscheduled programming visit is required to adjust stimulation parameters, in case of unexpected discomfort.

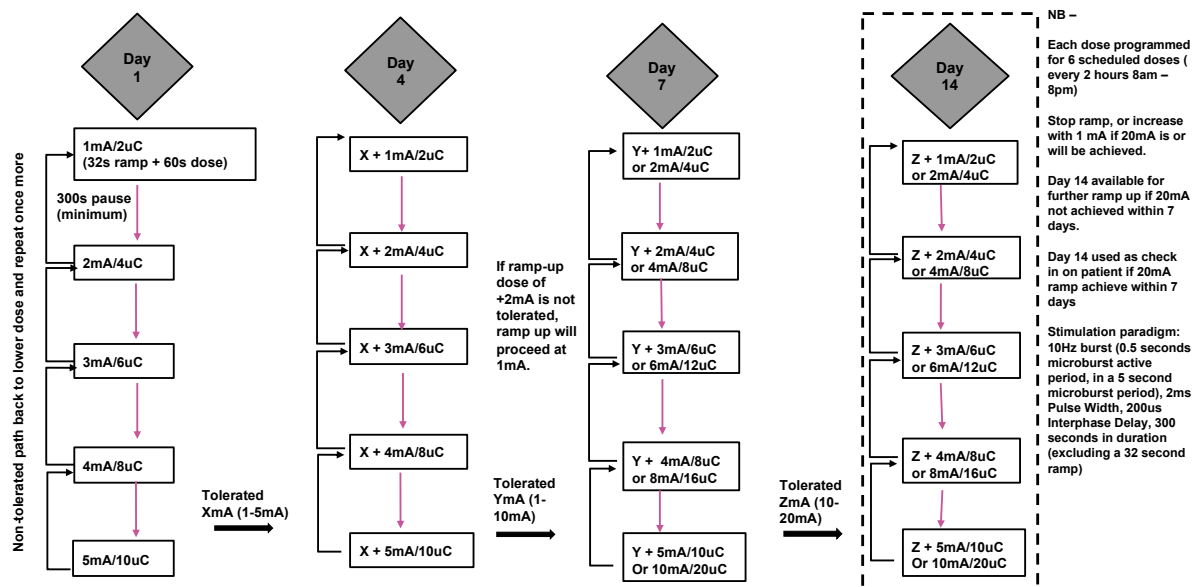


Figure 7. Schedule of dose escalation to max dose (20 mA), or to maximum tolerated dose, as defined by clinician and participant feedback. Illustration above assumes target dose is achieved after 3 or 4 visits¹. X = defined as maximum tolerated dose at end of day 1. Y = defined as maximum tolerated dose at end of day 4. Z = defined as maximum tolerated dose at end of day 7 (ideally 20 mA). Day 14 and 28 provides an additional day to ramp participants that have not yet achieved 20 mA or to check on participant if 20 mA was

achieved within 7 days. For ramp-up 0.5mA increments may be used in cases of low tolerability to stimulation

- 1. Additional dose escalation visits may be scheduled as needed, based on participants' feedback on tolerability of dose escalations, at PI's discretion and in consultation with the sponsor.*

7.8.3. ADAPTATION OF STIMULATION ON DAY 42 AND/OR 56

See for adaptation of the stimulation frequency and timing the decision tree in Figure 8. The number of stimulations can be adapted and/or night-time stimulation can be introduced following the principles below.

- On Day 42 assessment, if remission is not achieved as defined by the DAS28-CRP ≥ 2.6 , night-time stimulation may be introduced in those participants who do not experience discomfort during stimulation (i.e., 6 stimulations over 24 hours).
- If remission in these participants is not reached at Day 56, the total number of stimulations might be increased to 12 over 24 hours.
- On Day 42 assessment, if remission is not achieved and the participant does not tolerate night-time stimulation, the number of stimulation episodes can be increased to 12 episodes during day-time
- If the participant had not received night-time stimulation since Day 42, and will tolerate night-time stimulation at Day 56, night-time stimulation can be introduced by dividing the stimulations over 24 hours.

7.8.4. UNSCHEDULED VISIT

Unscheduled visits (those not aligned with the pre-specified visit schedule in Table 3) may occur as a result of unexpected discomfort experienced by the study participant, if the system is turned OFF, if new information suggests that a change in pre-specified stimulation parameters is required, or there is a need for system troubleshooting. If related to device troubleshooting, device check procedures will be performed and review of IPG log data, programming changes, and other assessments will be recorded on Case Report Forms associated with the visit. If the visit is disease or other related, appropriate assessments or treatments may be performed and recorded on the associated Unscheduled Visit form.

7.8.5. SYSTEM REVISION VISIT

7.8.5.1. NON-IMPLANTED SYSTEM COMPONENTS

Non-implanted components of the system (e.g., PR or Charger) may become non-functional, damaged or lost. If troubleshooting fails to resolve issues pertaining to the non-implanted components, these system components may be exchanged for new components during an unscheduled follow-up visit.

7.8.5.2. IMPLANTED SYSTEM COMPONENTS

In many cases, stimulation parameters may be programmed to correct for any noted participant discomfort or to maintain satisfactory system function. However, it is possible that an extra follow-

up procedure may be considered to adjust or replace an implanted component if the performance of the implanted system is unsatisfactory or if troubleshooting concludes that an implanted component is non-functional or displaced. The troubleshooting visit may require device programming, review of IPG log data (as outlined in the Device Check visit), or other imaging e.g. X-ray, ultrasound or CT to check if system components appear displaced compared to the X-ray taken perioperatively.

If troubleshooting and X-ray assessments suggest that system function may be restored by replacing the IPG, risk and benefit of replacing the IPG will be discussed among the Investigator, surgeon, and participant (with technical input from Galvani). If it is decided to proceed with IPG replacement, the surgery will be scheduled with appropriate support provided by Galvani, and the participant will be managed as in Section 7.4. If it is decided to not replace the IPG, then the system function will be programmed OFF and the participant will be followed for safety.

If it is found that system function can only be restored via replacement of the lead, or the entire system (both lead and IPG), then system function will be programmed OFF and the participant will be followed for safety. Galvani does not recommend replacement of the lead at this time.

7.8.5.3. TOTAL REMOVAL OF THE IMPLANTED SYSTEM

Galvani does not recommend that study participants undergo a surgical procedure to remove the implanted system components upon study withdrawal or study completion. If removal of the implanted components of the study device has been decided, Galvani will provide technical support and pay the cost of the surgery and associated medical care for a period of 10 years from when the study device was implanted. If during this 10-year period, the study device is approved for marketing by the EMA, and the participant's private health insurance will pay only a portion of the costs, Galvani will reimburse the participant for any out-of-pocket expenses associated with the surgery and medical costs that the insurance does not pay. Note that Galvani does not recommend system explantation until a minimum of 3 months has transpired since the implant procedure.

More specific instruction on removal or adjustment of implanted components is contained in the Surgical Manual. Explanted system components must be returned to the Sponsor.

7.9 MISSED STUDY VISITS

If due to unforeseen disruptions (e.g., global pandemic) participants may miss a scheduled in-person visit; then a remote visit via telephone, Skype, Facetime, or other appropriate virtual communication will be substituted for a visit to the clinic. During this visit the PI or delegate will discuss with the participant the disease activity according to the standard for remote visits in the clinic, including the perception and application of the stimulation therapy. Thereafter, the PI will discuss with the participant if she/he is comfortable to keep the stimulation ON and reschedule a follow-up visit. If the visit is within 2 weeks of the planned visit, the site staff will perform in-person procedures (e.g., blood sampling, device check, ECG as indicated in Table 3 and Table 7) according to the planned visit. If the re-scheduled visit is outside the 2 weeks time frame, the in-person procedures will be performed according to the following regularly-scheduled visit, and data collection for the planned visit will be abandoned.

If the participant wants to turn the stimulation OFF, or in the opinion of the PI the stimulation needs to be turned OFF, the participant will be re-instructed during the remote visit how to turn the device OFF and a follow-up visit will be scheduled as soon as feasible. The participant will be asked to keep charging the IPG.

If the participant has a missed study visit during the ramp-up period, the participant may maintain stimulation with the same parameters as scheduled during the last ramp-up visit, unless the PI and the study participant agree to turn the device OFF until the participant can return to the clinic. A follow-up visit will be planned as soon as possible. The participant will be asked to keep charging the IPG.

While a substitution of a remote visit will give rise to a protocol deviation due to missing in-person assessments, the remote discussion of disease activity and therapy will allow the PI to assess risk of harm to participants. If the PI perceives a potential for harm to participants from having a remote visit instead of an in-office visit, the PI may take additional appropriate and necessary steps to mitigate that harm in consultation with the Sponsor. These actions may be reported to the EC according to local expected time frames (Table 12 and Table 13).

7.10. EARLY WITHDRAWAL VISIT

For an Early Withdrawal Visit, all the assessments and procedures described for the Month 60 End of Study Visit (section 7.1, Table 7) should be performed.

8. DATA MANAGEMENT

Data management will be performed by a contract research organisation in accordance with Sponsor agreed standards and data cleaning procedures, as described in a study specific Data Management Plan, to ensure integrity of the data. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). CRFs and electronic data, including queries and audit trails, will be retained by the Sponsor and copies sent to the investigator to maintain as the investigator copy.

8.1. SOURCE DATA AND DOCUMENTS

Source data collection is the responsibility of the clinical staff at the site under the supervision of the investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRFs or entered in the CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data, and its origin can be found in the Source Data Agreement.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

8.2. DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., IPG logs, laboratory data). All electronic systems where data are stored include password protection and audit trails. The e-CRF includes internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Where data queries arise, the investigator will respond to clarify, confirm, explain or correct data issues as necessary.

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRFs. Guidance on completion of CRFs will be provided in CRF completion guidelines and Manual of Procedures.

The investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents. Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data. The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organisations).

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

The primary objective of this trial is to assess safety of the system implant (lead and IPG) as determined by the incidence of implant and device-related SAE's through 28 days as well as the safety and tolerability of splenic NVB stimulation therapy as determined by device-related SAE's from Day 1 until the end of the study.

9.1. SAMPLE SIZE

Sample size has been determined based on feasibility for this pilot study. No hypotheses will be tested, and no sample size calculations have been performed. The sample size of 5, has been determined to allow for evaluating safety without exposing too many participants to an implant.

9.2. POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined:

Table 10 *Analysis populations*

Population	Description
Screened	All participants who were screened for eligibility, including those participants who signed the informed consent form (ICF) but didn't pass screening.
Enrolled	All screened participants who passed screening and entered the study, including those participants who met all inclusion criteria during screening but weren't successfully implanted. Note screening failures are excluded from the Enrolled population as they didn't enter the study.
Implanted	All enrolled participants in whom a device was implanted.
Intent-to-Treat (ITT)	All participants in the Implanted population who received at least one active stimulation during the treatment period (i.e. from Day 1). The ITT Population will be used for all safety, efficacy and biomarker summaries for Period 1, unless otherwise specified in the Statistical Analysis Plan (SAP).
Long-Term Follow Up (LTFU); Period 2	All participants in the ITT population who continued into the LTFU period. The LTFU population will be used for all safety, efficacy and biomarker summaries for the LTFU period, unless otherwise specified in the SAP.

9.3. FINAL ANALYSIS

Safety analysis will be reviewed in an ongoing manner during the study, but no formal interim analyses will be performed.

This study will include two reporting periods – the Primary reporting period (triggered by the last participant's last visit in Period 1 [REDACTED] which will be associated with its own Clinical Study Report.

The analyses for Period 1 will be conducted when all participants have completed their last visit on Day 84. Safety data will be summarised descriptively and listed in tabular and/or graphical format. Efficacy and Biomarker data will be summarised and listed as appropriate with no formal statistical analyses performed.

A full description of the planned analyses for the study will be outlined in the SAP.

10. DEVICE DEFICIENCIES, ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS

10.1. DEVICE DEFICIENCY

10.1.1. DEFINITION

A device deficiency is defined as the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance, which may include device malfunctions, use errors and inadequate labelling.

10.1.2. REPORTING REQUIREMENTS

Device deficiencies will be documented on CRFs and are reported to the study sponsor and the MHRA/EC according to local regulations and according to this protocol. Investigators must characterise device deficiencies according to if they could have led to a serious adverse device effect (SADE).

10.2 ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS

10.2.1. DEFINITIONS

An adverse event (AE) is defined according to the European Standard EN ISO 14155 as ‘any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings)’ in participants, users or other persons, whether or not related to the investigational medical device. For users or other persons, this definition is restricted to events related to the investigational medical device.

In Period 2 (LTFU), adverse events that are neither serious nor device-related are not recorded in the eCRF.

The following are not considered adverse events:

- A medical, surgical, or diagnostic procedure itself; the condition that leads to the procedure is the adverse event.
- Pre-existing conditions present or detected at screening which do not worsen.
- Interventions for pretreatment conditions (e.g., elective surgery) or medical or diagnostic procedures that were planned before study enrollment are not considered adverse events; however, complications of such procedures which occur after enrollment are to be considered adverse events.

- Situations where there is no untoward medical occurrence, e.g., social or respite care admissions.

An adverse device effect (ADE) is an adverse event related to an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the operation, or any malfunction of the investigational medical device. This also includes any event that is a result of a use error, inadequate labelling or intentional abnormal use of the investigational medical device.

10.3. INVESTIGATOR CLASSIFICATION OF ADVERSE EVENTS

Investigators are responsible for categorising AEs according to their seriousness, severity and relatedness using the definitions that follow.

10.3.1. DEFINITION OF SERIOUSNESS

An adverse event (AE) is defined as a serious adverse event (SAE) if it:

- led to a death
- led to a serious deterioration in health of the participant, that either resulted in:
 - a life-threatening illness or injury, or
 - a permanent impairment of a body structure or a body function, or
 - in-patient hospitalisation or prolongation of existing hospitalisation, or
 - medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function,
- led to foetal distress, foetal death or a congenital abnormality or birth defect.

Note 1: Planned hospitalisation for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.

An adverse device effect (ADE) is considered a serious adverse device effect (SADE) if it resulted in any of the consequences characteristic of a SAE (defined above). SADEs are further divided into anticipated and unanticipated SADEs. Anticipated ADEs based on the known risks are listed Appendix II.

10.3.2. UNANTICIPATED ADVERSE DEVICE EFFECT

An unanticipated adverse device effect means any serious adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

10.3.3. DEFINITION OF SEVERITY

The investigator's assessment of severity of an AE may be determined according to the following categories:

- Mild – An event that is easily tolerated by the participant, requires minimal or no treatment and does not interfere with the participant's daily activities.
- Moderate – An event that causes a low level of inconvenience and interferes with normal daily activities.
- Severe – An event that prevents a participant's usual daily activity and may require systemic drug therapy or other treatment. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; and both AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

10.3.4. DEFINITION OF RELATEDNESS

Investigators must also categorise adverse events according to their relationship to the study device (including study implant / explant procedure), study procedure or disease (RA), based on clinical judgment.

- Study device related: An adverse event that satisfies the definition of an ADE
- Study procedure related: An adverse event that occurs due to a study procedure but is not device related.
- Disease (RA) related: An adverse event that is considered expected from the underlying condition or that is prevalent in the population that is being studied; therefore, they would not typically be considered related to the study device or procedure. These will be reported on either the AE or Disease Related Event form as follows.

The following have been specified as disease-related events (DREs) and will be reported on the DRE form:

- Events related to exacerbation of articular/peri-articular manifestations of RA (flare).

When either of the following conditions apply, the event must be recorded and reported on the AE form:

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.
- New onset or worsening of extra-articular manifestations of RA.

The degree of certainty about relationship will be graded using the categories below.

- a) Not related: The relationship to the device or procedures or disease can be excluded when:
 - a. the event is not a known side effect of the product category the device belongs to or of similar devices and procedures.
 - b. the event has no temporal relationship with the use of the investigational device or the procedures.

- c. the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible.
 - d. the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event.
 - e. the event involves a body site, or an organ expected not to be affected by the device or procedure.
 - f. the event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
 - g. harms to the participant are clearly not due to use error.
 - h. In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
- b) Unlikely: the relationship with the use of the device or with study procedures or disease seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- c) Possible: the relationship with the use of the investigational device or with study procedures or disease is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- d) Probable: the relationship with the use of the investigational device or with study procedures or disease seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
- e) Causal relationship: the event is associated with the investigational device or with study procedures or disease beyond reasonable doubt when:
 - a. the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
 - b. the event has a temporal relationship with investigational device use/application or procedures;
 - c. the event involves a body-site or organ that
 - i. the investigational device or procedures are applied to;
 - ii. the investigational device or procedures have an effect on;
 - d. the event follows a known response pattern to the medical device (if the response pattern is previously known);
 - e. the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);

- f. other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- g. harm to the participant is due to error in use;
- h. In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

10.4. SPONSOR CLASSIFICATION OF ADVERSE EVENTS

The sponsor will delegate the sponsor classification of adverse events throughout this study to the unblinded DSMB. Further details will be documented in the DSMB charter.

10.4.1. REPORTING REQUIREMENTS

Complete, accurate, and timely, reporting of safety information are mandated by regulatory authorities, and this study is conducted in accordance with these regulations. The Clinical Operations department at Galvani Bioelectronics will oversee the adverse event reporting in the study.

AEs will be documented on CRFs and are reported to the study sponsor and the MHRA/EC according to local regulations and according to this protocol. Information reported on the AE CRF includes a description of the event, date of onset, assessment of seriousness, relatedness of the event to study device(s), study procedure(s) or disease, actions taken as a result of the event including therapies and diagnostic tests, and the outcome of the event. Each AE will be followed until it is resolved, stabilised, otherwise explained; except at the end of the study whereupon only ongoing ADEs/SADEs will be followed until they are resolved, stabilised, otherwise explained.

The sponsor has identified a number of adverse events that may occur in the majority of participants and do not need to be reported as an AE or ADE unless it meets the criteria or SAE or SADE (See Table 11).

Table 11 *Anticipated events that do not need to be reported as an AE unless it meets the criteria of an SAE or SADE*

General responses to surgical stress (Day -28 to Day -10)	During stimulation (Day 1 to Last study visit)
Anaesthesia related nausea / vomiting	Sensations during stimulation that do not require an intervention
Low-grade fever (< 37.8 °C)	
Sleep problems (insomnia)	
Hypoxia	

Abnormal laboratory findings or post-operative recovery metrics that are deemed by the investigator to be clinically significant, are associated with signs and/or symptoms, or which require new therapy or adjustment in prior therapy, must be recorded as adverse events.

11. STUDY MANAGEMENT

11.1 SPONSOR AND MONITOR CONTACT INFORMATION

See the Manual of Procedures.

11.2 INVESTIGATOR RESPONSIBILITIES

The investigator is responsible for conducting the study in accordance with the signed CTA, this protocol, applicable laws, the latest version of the “Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects”, the ISO 14155, the EU Medical Device Regulation and any conditions of approval imposed by the reviewing Research Ethics Committee (REC) and/or Regulatory Authority. The investigator is responsible for protecting the rights, safety, and welfare of participants under the investigator’s care, which should prevail over interests of science. The investigator is also responsible for ensuring that IC is obtained in accordance with this protocol and local regulatory and institutional requirements. Investigators shall avoid improper influence on, or inducement of, the participant, study sponsor, monitors, or other parties associated with the study. The investigator or sub-investigator may request the presence of sponsor personnel at study-related procedures.

This study will be conducted by investigators who have experience and/or training conducting medical device clinical studies, and at least one investigator at the site has experience and/or training performing the surgical procedures referenced in this protocol. A Clinical Trial Agreement (CTA) must be signed by all parties named in the agreement and returned to Galvani prior to the commencement of any study activities at the centre.

11.2.1. RESEARCH ETHICS COMMITTEE MANAGEMENT

A copy of the written approval must be received by Galvani before recruitment of participants into the study.

The investigator must submit (or delegate responsibility to sponsor representatives), to obtain approval from the REC for all subsequent protocol amendments and changes to the ICF (as necessary). The investigator should notify the REC of deviations from the protocol or serious adverse events occurring at the site, and other adverse event reports received from Galvani, in accordance with local procedures.

The investigator is responsible for submitting progress reports to the REC, which must be agreed upon with Galvani prior to submission.

11.2.2. STUDY TRAINING

Center personnel (investigators, coordinators, other clinical staff) participating in the clinical study will be trained in study activities relevant to their role prior to conducting any study activities. Investigators and study coordinators will be trained on their responsibilities, study device usage and handling, electronic trial master file (eTMF) usage, CRF completion, and other study procedures in the protocol.

Training on Good Clinical Practices and on IC procedures will also be provided if documentation (including training outline) of a recent (within 3 years) training cannot be provided. Investigator and/or study coordinator will attend meeting(s) or conference call(s) to discuss the study protocol, training, study results, etc. In addition, the study surgeon will be trained on implantation of the Galvani System through cadaveric labs.

11.2.3. CENTER READINESS

The investigator (or designee) is responsible for forwarding or uploading to the eTMF the following documents to Galvani (or designee) for review before recruitment of participants can occur.

- Signed and dated protocol signature page, or acceptable e-signature via sponsor eTMF system
- Copy of the REC approval of the protocol and ICF
- Up to date curricula vitae of PI and all co-investigators and sub-investigators
- Signed Clinical Trial Agreement
- Completed Delegation of Duties log, that lists responsibilities of site personnel required to perform study activities according to the investigational plan
- Documentation of study training relevant and pertinent to the duties delegated by the investigator to personnel conducting study activities, and recent (within 3 years) training on good clinical practices (GCP); except for the hands-on training of study surgeons per 11.2.2
- Certifications / qualifications of laboratories involved in analysing study participant biological samples

Upon acceptance of the documents above, and upon obtaining regulatory and any other local approvals (as appropriate), Galvani will notify investigator that they may begin enrolment.

11.2.4. EQUIPMENT STORAGE, HANDLING AND TRACEABILITY RECORDS

The investigator must ensure secure storage for study-specific equipment and files, including electronic files. When equipment from Galvani arrives at the investigators site, the material is under the control of the investigator. Upon receipt, investigators will assure secure storage for equipment and other study-related materials (e.g., paper-based study records and forms). As a means of documenting control of equipment, equipment disposition forms will be provided to document the date of receipt of equipment, use, and (when applicable) disposal. Equipment used during study procedures (minimally equipment with serial numbers) will be documented on study procedure CRFs or equipment disposition forms. These forms will be reviewed on a regular basis during study monitoring. Devices supplied sterile will be tracked by lot number except for the lead and IPG, which will be tracked by serial number. All non-implanted single use items will be disposed of as per local policy after use unless there has been an adverse device effect, device deficiency or complaint reported with that item. In these cases, the items will need to be returned to Galvani. All unused equipment returned by a participant or system components explanted from a participant should be returned to Galvani and, when permissible by local laws and regulations.

11.2.5. PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical study protocol, local laws or regulations, or GCP. The noncompliance may be either on the part of the participant, the investigator, or the study

site staff. The investigator must refrain from implementing any modifications to the protocol without agreement from the sponsor, the REC and Regulatory Authorities (as applicable), except in cases when a deviation is necessary to protect the life or physical wellbeing of a participant in an emergency. Prior approval is not expected in situations where unforeseen circumstances are beyond the investigator's control (e.g., missed visits by participants, inadvertent mistakes, equipment failures, participants physically unable to perform required testing).

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations. All protocol deviations will be entered into the Protocol Deviation CRFs and reported to the study sponsor. Protocol deviations will be listed in the progress report to the REC. Protocol deviations must be reported immediately to the REC when the participant was put at risk. The site investigator is responsible for knowing and adhering to the reviewing REC requirements.

As a result of deviations, corrective actions are to be developed by the site (in collaboration with the sponsor) and implemented promptly.

11.2.6. INVESTIGATOR RECORDS

The investigator is responsible for retaining the records listed below. The following records document evidence of study conduct and may be subject to inspection by local or national regulatory authorities.

- All protocols and amendments
- IB and any amendments
- Manual of Procedures
- Current curriculum vitae for all investigators, (with signature and date)
- Delegation of Responsibilities Log
- All significant correspondence with sponsor, monitors, REC or MHRA, including required reports that pertain to this study
- REC roster or other documentation that REC approval of protocol was independent of investigator influence
- REC approvals
- National Regulatory Authority (e.g., MHRA) approval / waiver (as required)
- Signed Clinical Trial Agreement
- Sponsor Clinical Trial Insurance Certificate
- Study device disposition log, including shipping records
- Sample of the approved ICF and amendments
- Signed participant ICFs
- All CRFs and supporting data (e.g., hospital records or paper source documentation)
- Study site personnel training records
- Laboratory certification or accreditation, including normal values/ranges for relevant clinical laboratory tests.
- Maintenance and calibration of equipment relevant to study assessments are performed and documented
- Documents supporting adverse event, device deficiency, study deviation reporting
- Interim reports
- Participant screening

- Communication of Monitor findings

11.2.7. INVESTIGATOR REPORTS

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all CRFs, all deaths and reportable adverse events and any deviations from the protocol. Original source documents should remain at the center in the medical record or in physical participant files.

Table 12 *Investigator Reports*

Report	Submit To	Constraints
SAEs and SADEs that are related to the study and unexpected, and new findings/updates in relation to already reported events	Sponsor	Within 3 calendar days after learning of the event
	REC	Within 15 days after learning of the event.
Device deficiencies that could have led to a SADE	Sponsor	Within 3 calendar days after learning of the event
	REC	Within 15 days after learning of the event.
Urgent Safety Measures (e.g., deviation from the protocol to protect participants against any immediate hazard to their health or safety without prior authorisation from regulatory body	Sponsor	Within 24 hours after learning of the event
	REC	Immediately and in any event within 3 days)
Adverse Device Effect (ADE)	Sponsor	Promptly after learning of the event.
Data Security Incident ¹	Sponsor	Without undo delay = within 12 hours of learning of the event
Withdrawal of EC approval	Sponsor	Promptly after learning of the event, but no longer than 5 working days
	All study participants	Promptly
Report	Submit To	Constraints
Study suspension or early termination	REC	Within 15 days
	All study participants	Promptly

Report	Submit To	Constraints
Progress reports	REC	Annually (starting 12 months after the date of favourable opinion)
End of study notification	REC	Within 90 days
Summary of final report	REC	Within 1 year of the conclusion of the research (defined as end of study as per this protocol).

1. Data Security Incidents include loss, alteration, unauthorised disclosure of, or access to personal data as defined in the General Data Protection Regulation (GDPR); this reporting timeline is to support the Sponsors reporting obligations under the GDPR in case of a reportable data security breach.

11.2.8. STUDY RECORDS RETENTION

Records and documents, including signed IC, pertaining to the conduct of this study must be retained by the investigator for 20 years from the issue date of the Clinical Study Report / Summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. Assistance arranging for the archiving of study data may be requested of the study sponsor, if necessary.

11.2.9. MEDICAL CARE OF PARTICIPANTS

The investigator is responsible for the following:

- Medical care of study participants during the study, and for care of ongoing adverse events
- Instructing participants on study procedures, including use of devices
- Informing participants of the nature and cause of any adverse events, and of significant new findings that may require additional medical care
- Instructing participants on what to do if emergency medical care is needed during the study
- Recording study enrolment in the participants' medical records, and forming their personal physician (with their approval, and if regulations allow).

11.3. SPONSOR RESPONSIBILITIES

Galvani Bioelectronics will serve as the Sponsor of this study and provide the funding required. A Sponsor is an individual or organisation that takes responsibility for initiating or implementing a clinical study. The sponsor shall avoid improper influence on, or inducement of, the participant, study monitor, investigator, or other parties associated with the clinical study.

11.3.1. SPONSOR SUPPORT

Sponsor representatives will participate in the conduct of the study to the extent described below. Participation in the study will be limited to Sponsor personnel who are appropriately qualified

and trained, such as those personnel with an engineering, technical or nursing degree or equivalent training, or significant experience in the active medical device industry.

Galvani FCEs will be delegated responsibility for programming the device using the CP through the Day 84 visit. Galvani personnel may provide technical support to the investigator, and other site personnel who are members of the investigators team. Support may include training, addressing site personnel questions, or providing clarifications concerning the operation of the PR or CP. Galvani will provide a surgeon proctor to support at least the first implant at the site.

11.3.2. EQUIPMENT DISTRIBUTION

The Sponsor will distribute investigational devices to a site when all requirements for study site activation have been met. Other equipment and supplies provided by the Sponsor or delegate will be distributed to a site only after the site is trained on equipment storage and traceability requirements.

11.3.3. CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of study participants are protected; that the reported study data are accurate, complete, and verifiable; and that the conduct of the study is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). It is the responsibility of the study sponsor, Galvani Bioelectronics, to ensure that proper monitoring of the study is conducted, and that REC and MHRA review and approval of the investigation is obtained. Trained personnel appointed by the study sponsor will conduct monitoring activities on behalf of Galvani.

During monitoring visits any new and previous findings (ongoing or resolved) and recommended preventive/corrective actions will be communicated with the study personnel and will also be addressed in a follow-up letter that will be sent to the study centre personnel after the visit. A study closure visit may be conducted at the end of the study to review record retention requirements, equipment disposition requirements, etc., with site personnel. A telephone contact may take the place of a study closure visit if appropriate (e.g., low participant enrolment, recent monitoring visit, etc.).

11.3.4. SECURING COMPLIANCE

In the event of repeated noncompliance, as determined by Sponsor management, a Sponsor monitor or Sponsor representative will attempt to secure compliance by visiting, telephoning and/or corresponding with the investigator. If the investigator is found to be repeatedly noncompliant with the signed Investigator Agreement, the study protocol, applicable regulatory requirements, or any other conditions of the study, Sponsor will either secure compliance or, at its sole discretion, terminate the investigator's participation in this study. In the event of termination of investigator participation, study equipment and material will be returned to Sponsor, unless this action would jeopardise the rights, safety, or welfare of the participants.

11.3.5. SPONSOR RECORDS

Galvani will maintain the following accurate, complete, and current records:

- Protocol and any amendments
- IB and any amendments
- Current curriculum vitae for all investigators (with signature and date)
- Curriculum vitae of other individuals who contribute to the study (e.g., monitors).
- Delegation of responsibilities log
- All significant correspondence with the investigator(s), site staff, and monitors
- REC roster or other documentation that REC approval of protocol was independent of investigator influence
- REC approvals and renewals documentation
- National Regulatory Authority approval / waiver (as required)
- Signed CTAs
- Signed agreements with third parties (e.g., CRO's)
- Insurance certificate
- Shipping records for study-related equipment, and physical documents
- Sample of approved ICF and amendments
- All monitoring reports
- Names and contact information of monitors
- Blank CRFs to evidence content of data being collected
- Completed CRF's or electronic CRF's submitted by site personnel
- Electronic data acquired outside of CRFs
- Study site personnel training records and training records of Galvani personnel involved in the study
- Laboratory certification or accreditation, including normal values/ranges for relevant clinical laboratory tests.
- Statistical analyses and supporting data
- Documents supporting adverse event, device deficiency, study deviation reporting
- Progress reports, and final report

11.3.6. SPONSOR REPORTS

Galvani will assist the investigator with reports to the REC as needed and oversee that these requirements are being met.

Table 13 *Sponsor Reports*

Report	Submit To	Constraints
SAEs, SADEs, DD that could have led to a SADE and new findings/updates in relation to already reported events	Investigators	At timelines appropriate for perceived risk, or as required by local regulations.
	Regulatory Authority	For those that indicate an imminent risk of death, serious injury, or serious illness and that requires remedial action for other participants, users or other persons or a new finding to it, within 2 calendar days after learning of the event or new finding. For all other SAEs no later than 7 calendar days after learning of the event or new finding.
Significant new information that may impact safety or conduct of the study	Investigators	Prompt notification.
	Regulatory Authority	Prompt notification.
	Participants	As approved by the REC (which may require signature on an updated and REC approved ICF).
Serious breach in GCP or protocol	Regulatory Authority	Within 7 days of becoming aware
Personal Data Breach 1	National Supervisory Authority; Investigator	Within 72 hours of awareness
Study Suspension and Premature Termination	Investigators	Prompt notification and reason(s)
	Regulatory Authority	Within 15 days
End of Study Notification	Investigators	Prompt notification and reason(s)
	Regulatory Authority	Within 90 days

Report	Submit To	Constraints
Progress reports	Investigators	Support progress report submission by investigator to REC at required timelines (yearly at minimum)
Final report	Investigators	Within 1 year of study completion
	Regulatory Authority	Not mandated but can be requested

11.3.7. STUDY RECORDS RETENTION

Records and documents pertaining to the conduct of this study must be retained by the sponsor for 20 years from the issue date of the Clinical Study Report / Summary.

11.4. PARTICIPANT CONFIDENTIALITY

11.4.1. CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorised third party without prior written approval of the sponsor. Study data collection, processing, use, and storage will be consistent with EU regulations (Regulation 2016/679 General Data Protection Regulation). All research activities will be conducted in as private a setting as possible.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the IC.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored in secure electronic clinical databases. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique participant identification number. The data will be pseudonymised. The ID of the research participant for GAL1039 study is a combination of location number (2 digits) and patient number (3

digits): XX-XXX and is assigned upon registration. Investigators will keep a log of participants enrolled in the study along with the unique identification number and store this log in a secure location to protect the personal identity of participants. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

11.4.2. FUTURE USE OF DATA AND BLOOD SAMPLES

The sponsor will use data collected from study participants to conduct the research specified in this protocol. In addition, the data may be used for further research, provided consent is indicated in the ICF. Further research falls outside of the objectives of this study and could include for example investigations into other diseases.

Blood samples may be stored for up to 5 years from study end at the Research Centre or at a central repository. These may be used for other (future) research in the field of splenic nerve stimulation or further development of the treatment method provided consent for other (future) research is indicated in the ICF. After this period any remaining samples will be destroyed.

11.5. STUDY CLOSURE

Normal study completion occurs when the last visit of the last participant in the study is completed. Upon study termination or completion, the sponsor and investigator will collaborate to complete all data forms and resolve any queries, and complete study records (e.g., device disposition). At the sponsor's request, an investigator will return sponsor-owned study devices in his/her possession. The investigator will comply with study termination / completion reporting timelines.

The sponsor and investigator(s) will collaborate on the final study report (when possible). The investigator and sponsor will each sign and date the final report to indicate agreement with its content.

11.6. PUBLICATION POLICY

This clinical study will be registered in a publicly accessible database (e.g., clinicaltrials.gov) and the results of this study will be made publicly available (via posting on a publicly accessible database and/or scientific journal), regardless of outcome, no later than 12 months after the end of the study (defined as closure of the database). The investigator agrees to submit all manuscript or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Detailed information on the publication policy and authorship are set out in section 11 of the Clinical Trial Agreement between the Sponsor and Investigator.

11.7 COMPENSATION FOR INJURY

The sponsor has a WMO subject – and a liability insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). The insurance provide cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

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APPENDIX I FERTILITY DEFINITIONS, CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Woman of Non-childbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
 - a. Documented hysterectomy
 - b. Documented bilateral salpingectomy
 - c. Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal female

- d. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
 - i. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
 - ii. Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

1. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

2. Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods (for the purpose of this study) include:

3. Documented hysterectomy
 4. Documented bilateral salpingectomy
 5. Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

CONTRACEPTIVES^a ALLOWED DURING THE STUDY INCLUDE:
• Highly Effective Methods^b That Have Low User Dependency <i>Failure rate of <1% per year when used consistently and correctly.</i>
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation^b
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)^b
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) <i>Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.</i> Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• Highly Effective Methods^b That Are User Dependent <i>Failure rate of <1% per year when used consistently and correctly.</i>
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation^c – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation^c – oral – injectable
• Sexual abstinence <i>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.</i>
• Effective Methods^d That Are Not Considered Highly Effective <i>Failure rate of ≥ 1% per year when used consistently and correctly.</i>
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide^e
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)

- a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
- b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
- c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
- d) Considered effective, but not highly effective - failure rate of $\geq 1\%$ per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.
- e) Male condom and female condom should not be used together (due to risk of failure from friction).

Female Participants who become pregnant

- The stimulation - if set to ON - will be set to stimulation OFF, and if the participant is in period 1, 2 or 3 they will enter period 4 to be followed for safety.
- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- The initial information will be recorded on the appropriate form and submitted to Galvani within 24 hours of learning of a participant's pregnancy.
- Participant will be followed until at least 8 weeks post-delivery to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to Galvani
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to Galvani. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

APPENDIX II POTENTIAL ADVERSE EFFECTS INHERENT TO THE SURGICAL PROCEDURE, PRESENCE OF THE SYSTEM OR SYSTEM USE

Potential Adverse Device Effects due to surgery for system implantation (30 day perioperative period):

Potential Adverse Device Effects due the presence of the system or system use (alphabetical order):

Bleeding due to direct surgical trauma (mechanical or energy related)	Cardiovascular effect For example: hemodynamic changes including arrhythmias.
Cardiovascular effect - For example: hemodynamic changes including arrhythmias. - Myocardial infarction and stroke	Excessive fibrosis at neural interface
Colon injury – surgical injury (mechanical or energy related)	Foreign body response (temporary or permanent immune response to medical device)
Esophageal injury – direct surgical trauma (mechanical or energy)	Gastric injury
Gastric injury – surgical trauma (electrical energy or mechanical injury)	Infection
Hernia (delayed presentation) – trocar site (external) and Internal (gastrocolic omentum and gastro-hepatic ligament)	Nerve injury (primarily splenic)
Infection	Organ constriction/damage (not otherwise specified)
Nerve injury (primarily splenic and peripheral nerves)	Off-target stimulation effect
Organ constriction/damage	Pain
Pain	Pseudoaneurysm – delayed presentation of direct surgical trauma (mechanical or energy)
Pancreatic injury	Splenic injury
Pseudoaneurysm	Stenosis - Vascular stenosis or obstruction, Gastrointestinal tract stenosis or obstruction
Small intestine injury	Tissue damage
Splenic injury	Unwanted immunosuppressive effect
Stenosis	
Thrombosis (Venous thromboembolic event)	
Tissue damage	
Unaesthetic cosmesis (requiring intervention)	

APPENDIX III VERSION HISTORY GAL1039 PROTOCOL

Version Protocol	Change description	Effective Date/REC response	Comment
Version 1.0		31 May 23	
	NA		First version submitted
Version 2		02 Aug 23	
Section 5.6.5	Section 5.6.5 moved up to section 5.6.4		Section moved up to section 5.6.4 due to adding a new subheading "5.7 Clinical stopping criteria."
Section 5.7	A sub heading was added for section 5.7.1 "Implantation Procedure Hold & Study Suspension or Early Termination". In this section additional language was added to make a reference to Section 12.2 of the Clinical Trial Agreement, describing reasons for premature termination as laid out in the CCMO Directive on the Assessment of Research Contracts (Art. 3).		Change incorporated upon question METC.
Section 5.7.2.	Section 5.7.2." individual participant investigational product stopping criteria" added.		Change incorporated upon question METC.
Section 7.8.5.3	MHRA replaced by EMA		Error spotted during review
Section 11.4.1.	Explained what code will be used to pseudonymized the data.		Added upon question METC
Section 11.6	Reference to detailed information on the publication policy and authorship as laid out in the CCMO Directive on the Assessment of Research Contracts (Art. 4).		Change incorporated upon question METC

	Sentence on "Publication no later than 12 months after close of trial" added.		
Section 11.7	Section 11.7 "Compensation for injury" added.		Added upon request METC
Version 3.0		16 Oct 23	
Section 4.2, Figure 6	Figure 6 replaced; reference to "SHAM Stim" removed.		Error spotted after internal review in schematic presentation of the study; In error "SHAM stimulation" was mentioned in Peeriod 1.
Section 5.2	Added the following surgical exclusion criteria: a Direct contact between the splenic artery and the splenic vein, in the area identified for cuff placement; b. Prior pancreatic resection. C Splenic pathology (e.g. splenic abscess, malignancy, prior embolization or vascular anomalies that distort local anatomy).		Surgical exclusion criteria updated in line with Surgical Implant Manual as requested by METC.
Section 11.7	Liability insurance added		On request of METC
Version 4.0		18 Jun 24	
Protocol	Correcting small error's throughout document.		Version approved 03 OCT 24
Section 3.2	Feedback Clinician on Galvani system components removed for Period 1 since the FCEs are supporting the visits and Clinicians have not enough exposure to the system in Period 1.		
Section 3.6	Removed all objectives related to "Change from day of last change in Therapy...." after re-evaluation this did not make sense as an objective for a 5 patient's study.		
Section 4	Section 4.1 and throughout the protocol:		

	- Ramp-up reduced to Day 28. In error the ramp-up period was extended to Day 56, since this interferes with the objective of the study to test introducing night - time stimulation and/or increase number of stimulations on Day 42 and Day 56, this is corrected throughout the protocol. - The change in number of stimulations and introducing night-time stimulations is more clearly described throughout the protocol. Section 4.2: Figure updated to reflect ramp-up until Day 28. Section 4.2.2: The change in number of stimulations and introducing night-time stimulations is more clearly described Section 4.2.3. Window for taking CT-angiogram at start of Period 2 indicated. Section 4.5: Risk of Clinical Significance: Potential Risk related to the Galvani System section updated to include potential loss of therapy risk due to device using more energy than normal.		
Section 6	Section 6.1 : The change in number of stimulations and introducing night-time stimulations is more clearly described		
Section 7	Table 3: Error's in relation to ramp-up and adaptation of stimulation updated in table of assessments. Section 7.8.3: The change in number of stimulations and introducing night-time stimulations is more clearly described. Section 7.6.6: Explaining collection of certain types of AEs in Period 2 more clearly. Section 7.8.2: Dose may also be increased with a half step (0.5 mA), but was in error not added in the protocol. Now added		
Version 5.0		08 OCT 2024	
Abbreviations	Updated to align with updated text		
Section 5.5	Updated permitted and prohibited therapies to allow conditional MRI assessments		