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Galvani Bioelectronics

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

GAL1039

Statistical Analysis Plan

Version 2.0

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Version History

Version	Version Date	Author/Title	Summary of Key Changes
1.0	26SEP2021	Lisa Thackeray/Sr Principal Biostatistician	Initial Release
2.0	20JAN2025	Jason Viehman/ Senior Biostatstician	Updated to align with Protocol V11, including the following key updates: - Inclusion of Long-Term Follow Up (LTFU) period. Period 1 now defines the start of study to end of Day 84 visit. Period 2 defines the LTFU period. - Updates to the Schedule of Assessments.

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Document Approval

This statistical analysis plan has been read, reviewed and approved by the individuals listed in the table below. The approval electronic signatures and date of signing is held within the audit trail of the sponsors electronic Trial Master File (eTMF).

Authors
V1: Lisa Thackeray, Sr. Principal Biostatistician, NAMSA
V2: Jason Viehman, Senior Biostatistician, NAMSA

Reviewers
Phil Milliken, Clinical Development Director, Galvani Bioelectronics
Olaide Raji, Statistics Leader, GlaxoSmithKline
Shannon Springer, Regulatory Director, Galvani Bioelectronics
Christopher DeMorett, Clinical Lead Director, Galvani Bioelectronics
Tian Zheng, Clinical Development Operation Manager, Galvani Bioelectronics

Approval
Carly Barnett, Associate Director, GlaxoSmithKline
Margriet Vervoordeldonk, Sr Director and Clinical Lead, Galvani Bioelectronics
Isha Gupta, Translation and Engineering Group, Galvani Bioelectronics
Raolat Abdulai, Chief Medical Officer, Galvani Bioelectronics

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1 Introduction

This statistical analysis plan (SAP) describes the planned statistical methods to be used during the reporting and analysis of data collected under the Clinical Investigation Protocol *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* (GAL1039).

This SAP should be read in conjunction with the study protocol, case report forms (CRFs), and other applicable documents listed in Table 1.

This version of the SAP has been developed with respect to GAL1039 Protocol Version 11.0 and Version NL 5.0. Any revisions to the protocol or CRFs that impact the planned analyses may require updates to the SAP.

Table 1: Applicable Documents:

Document Number, Version	Document Title
GAL1039 VV-TMF-03656, V11.0	GAL 1039 Protocol; 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.
GAL1039 VV-TMF-04417, NL V5.0	GAL 1039 NL Protocol; 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.
VV-TMF-00754, V1.0	GAL1039 SRS
VV-TMF-01352, V6.0	GAL1039 Manual of Procedures
VV-TMF-01038, V4.0	DSMB Charter for Galvani Clinical Studies
VV-TMF-01445, V1.0	North Glasgow_Biochemistry User Manual Including Reference Ranges
VV-TMF-01446, V1.0	North Glasgow_Haematology User Manual Including Reference Ranges
VV-TMF-4523, V19	GAL1039 Site 003 AMC Lab Normals
VV-TMF-4524	GAL1039 Site 003 AMC Lab Normals, email

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2 Abbreviations

Abbreviation/Term	Definition
ACR	American College of Rheumatology
ADEs	Adverse Device Effects
AEs	Adverse Events
ALT	Alanine Aminotransferase
AMC	Amsterdam UMC
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CDAI	Clinical Disease Activity Index
CP	Clinician Programmer
CRF	Case Report Form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DAS28-CRP	28 Joint Disease Activity Score-CRP
DD	Device Deficiency
DI	Disease Index
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EULAR	European Alliance of Associations for Rheumatology
HAQ-DI	Health Assessment Questionnaire Disability Index
HR	Heart Rate
HRQL	Health-related quality of life
IC	Informed Consent
ICF	Informed Consent Form
IL-6	Interleukin-6
IPG	Implantable Pulse Generator
ITT	Intent to Treat
LPS	Lipopolysaccharide
LTFU	Long Term Follow-Up
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCS	Mental Component Score
MCV	Mean Corpuscular Volume
MHRA	Medicines & Healthcare products Regulatory Agency
NRS	Numerical rating scales

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NVB	Neurovascular Bundle
PCS	Physical Component Score
PhGA	Physician's Global Assessment of Arthritis
PR	Patient Remote
PtGA	Patient's Global Assessment of Arthritis
RA	Rheumatoid Arthritis
RAID	Rheumatoid Arthritis Impact Disease Questionnaire
RBC	Red Blood Cell
SADEs	Serious Adverse Device Effects
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SDAI	Simple Disease Activity Index
SF-36	Medical Outcomes Study Short-Form 36
SRS	System Requirement Specifications
TNF α	Tumor Necrosis Factor Alpha
VAS	Visual Analog Scale
WBC	White Blood Cell

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3 Changes to the Protocol defined Analysis Plan

Changes to the protocol-defined analysis plan will be listed here.

The following supporting outcome measures will be derived and listed for each participant at Day 84: achievement of ACR20/50/70.

4 Objectives and Endpoints

All study objectives and endpoints are specified in section 3 of the protocol.

4.1 Period 1 Open Label Phase

Objectives and endpoints for which planned summaries and analyses are described in this document are detailed in Table 2 for Period 1:

Table 2 Objectives and Endpoints for Period 1

Objectives Period 1	Endpoints Period 1
Primary Objective	Primary Endpoints
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). At Protocol specified visits throughout Period 1: - Laboratory Safety Assessments (clinical chemistry and haematology) - Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature) 12-Lead electrocardiogram (ECG) monitoring
Secondary Objectives	Secondary Endpoints
To evaluate the effect of splenic NVB stimulation on the change in pharmacodynamic and response biomarkers	Changes from baseline (Day 1, Period 1) in the levels of LPS-inducible cytokine/ chemokine release, including TNFα, IL-6, IL-8 and IL-17, in whole blood assay at protocol specified visits
To assess the usability of the clinician and patient external devices	Participant's feedback on the use of PR, Charger, Belt and Adhesive patch using sponsor-developed questionnaires

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Objectives Period 1	Endpoints Period 1
- To evaluate participant's perception of therapy - To assess the device performance	- Participant's feedback using a sponsor-developed questionnaire - The tabulation of device deficiencies (DD)
Exploratory Objectives	Exploratory Endpoints
To evaluate the efficacy of splenic NVB stimulation on clinical signs and symptoms	At Protocol specified visits throughout Period 1: - Change from baseline (Day 1) in the Simple Disease Activity Index (SDAI) - Change from baseline in DAS28-CRP - Change from baseline in Clinical Disease Activity Index (CDAI) - nACR improvement, defined as the lowest value of (% improvement of tender joint, swollen joint, median % improvement of the 5 remaining measures) - Proportion of participants achieving a moderate/good EULAR response - Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) score - Change from baseline in physical and mental component scores and domain scores of SF-36 - Change from baseline in quality of life as measured by Rheumatoid Arthritis Impact Disease Questionnaire (RAID) <i>Note: For composite endpoints each component of the assessment will also be reported. The changes from baseline over time will also be reported.</i>
To evaluate the effect of <u>intraoperative</u> splenic NVB stimulation on target engagement	- Impedance as measured by the IPG before and after stimulation. - Measurement of the heart rate (HR) before, during and after stimulation: <i>Change in HR from prior to stimulation to HR during and after stimulation.</i> - Measurement of the systolic blood pressure (SBP) before, during and after stimulation:

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Objectives Period 1	Endpoints Period 1
	<i>Change in SBP from prior to stimulation to SBP during and after stimulation.</i>

In addition to the protocol-defined endpoint of nACR, the following supporting outcome measures will be derived and listed for each participant:

- Achievement of ACR20/50/70

Summaries and analyses for the following additional exploratory objectives and corresponding endpoints won't be described in this document but will be described and reported separately by Queen Mary University of London or the University of Glasgow:

- Exploratory Objective: To evaluate signatures and dysregulated immune responses that predict treatment responses, and changes in signatures that occur during treatment, as assessed by the following, at protocol specified visits:
 - Change from baseline (Day 1, Period 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
 - Change from baseline (Day 1, Period 1) in distribution and phenotypes of cell subsets in whole blood
 - Change from baseline (Day 1, Period 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 (excluding epigenetic changes)

4.2 Period 2 Long Term Follow Up Phase

Objectives and endpoints for which planned summaries and analyses are described in this document are detailed in Table 3 for Period 2.

Table 3 Objectives and Endpoints for Period 2

Objectives Period 2	Endpoints Period 2
Primary Objective	Primary Endpoints
• To evaluate the long term safety and tolerability of chronic implant and if applicable active stimulation of	• Incidence, causality and severity of AEs, SAEs, ADEs and SAEs throughout Period 2 At Protocol specified visits throughout Period 2:

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Objectives Period 2	Endpoints Period 2
the splenic NVB with the Galvani System when used in conjunction with standard of care therapies including csDMARDs, with or without bDMARDs or tsDMARDs	- Laboratory Safety Assessments (clinical chemistry and haematology)¹ - Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature)¹ 12-Lead electrocardiogram (ECG) monitoring¹
Secondary Objectives	Secondary Endpoints
To assess the usability of the clinician and patient external devices¹	- Patient feedback on the use of PR, IPG Charger, Belt and Adhesive patch using sponsor-developed questionnaires¹ - Clinicians' feedback on the use of CP, PR, Charger, Belt and Adhesive patch using sponsor-developed questionnaires¹
To evaluate participant's perception of therapy¹	Participant's feedback using a sponsor-developed questionnaire¹
To assess the device performance	The tabulation of DDs throughout Period 2
Exploratory Objectives	Exploratory Endpoints
To determine whether the participants who achieved an initial clinical response to stimulation in Period 1 (> 1.2 improvement in DAS28-CRP at Day 84 versus baseline), but failed to achieve a DAS28-CRP ≤ 2.6, can improve clinical response upon stimulation for an additional 12 weeks¹	Number of participants achieving DAS28-CRP ≤ 2.6 at Month 3 of Period 2¹
To determine whether the participants who did not achieve a clinical response to stimulation in Period 1 (<1.2 improvement in DAS28-CRP at Day 84 versus baseline) can improve clinical response by	Number of participants achieving DAS28-CRP ≤ 2.6 at Month 6 of Period 2¹

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Objectives Period 2	Endpoints Period 2
adding a cs, ts or bDMARD medications in addition to the stimulation therapy ¹	
To evaluate the efficacy of splenic NVB stimulation on clinical signs and symptoms¹	- Change from baseline (Day 1, Period 1) in SDAI¹ - Change from baseline (Day 1, Period 1) in DAS28-CRP¹ - Change from baseline (Day 1, Period 1) in CDAI¹ - nACR improvement from baseline (Day 1, Period 1), defined as the lowest value of (% improvement of tender joint, swollen joint, median % improvement of the 5 remaining measures)¹ - Proportion of participants achieving a moderate/good EULAR response¹ - Change from baseline (Day 1, Period 1) in HAQ-DI¹ - Change from baseline (Day 1, Period 1) in physical and mental component scores and domain scores of SF-36¹ - Change from baseline (Day 1, Period 1) in quality of life as measured by RAID¹ <i>Note: For composite endpoints each component of the assessment will also be reported. The changes from baseline over time will also be reported.</i>

¹ assessments not applicable for participants with device in hibernation mode, i.e. not receiving stimulation

Summaries and analyses for the following exploratory objectives and corresponding endpoints won't be described in this document but will be described and reported separately by Queen Mary University of London or the University of Glasgow:

- Exploratory Objective: To evaluate biomarkers involved with cartilage and bone catabolism/metabolism as assessed by:
 - Change from baseline (Day 1, Period 1) at protocol specified visits
- Exploratory Objective: To evaluate biomarkers of efficacy which will be defined and selected from Period 1 as assessed by:
 - Change from baseline (Day 1 Period 1) at protocol specified visits

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5 Study 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 (6 week screening period, 4 weeks recovery from surgery and a 3 month 'treatment' period) and 5 years in Period 2.

Implant procedures will be temporarily halted after the first participant. Once this participant reaches Day 14 of stimulation in Period 1, 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.

A schematic presentation of the study design is shown below in Figure 1.

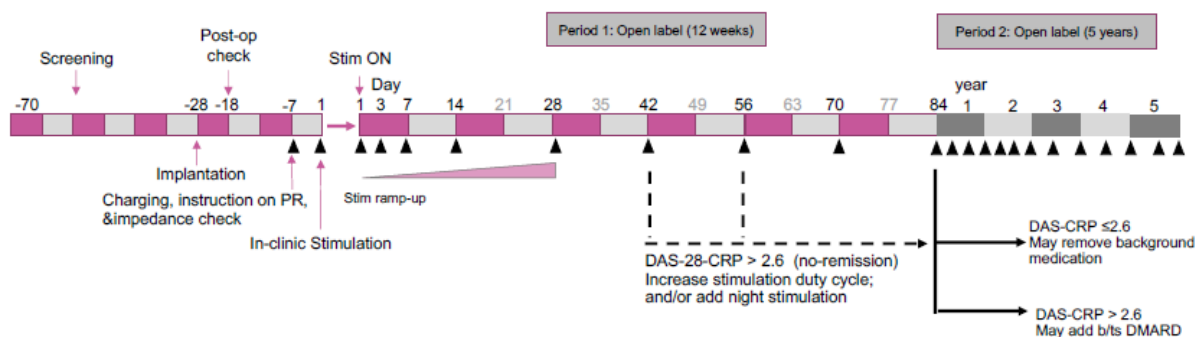


Figure 1.

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.

* All participants who are implanted with the Galvani system, and who either complete Period 1, Day 84, or withdraw from the study (discontinue stimulation) and are followed in Period 1 for safety only, will proceed to Period 2. More details are given in Section 6.4 of the Protocol.

5.1 Study Assessments

Please refer to Section 7.1 of the protocol for the schedule of activities to be performed during the course of the study.

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6 Sample Size Determination

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.

7 Statistical Analyses

7.1 General Considerations

All statistical analysis will be conducted using SAS version 9.4 or later (SAS Institute Inc., Cary, NC) or other widely-accepted statistical or graphical software as required.

Except where otherwise specified, the following general principles apply to the planned statistical analyses.

If the device was placed into hibernation, only safety data will be used from that point on, but efficacy data will be used for all data prior to device hibernation

7.1.1 Descriptive Statistics

Continuous data will be summarized with number of evaluable observations, mean, standard deviation, median, minimum and maximum.

Categorical variables will be summarized with frequency counts.

7.1.2 Baseline Assessments

For intraoperative cardiovascular assessments (heart rate and systolic blood pressure) a participant's baseline value will be defined as the average of their pre-stimulation values.

For all other endpoints (unless otherwise stated):

- Baseline will be the last assessment performed/taken prior to stimulation on Period 1 Day 1. If the pre-stimulation data on Day 1 aren't available, then the baseline will be set to missing.

7.1.3 Study Day

Study day will be calculated relative to active stimulation start date (Day 1), as follows:

If Assessment Date is prior to Day 1, Study Day = Assessment Date – Day 1 Date

If Assessment Date is on or post Day 1, Study Day = Assessment Date – Day 1 Date + 1

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Note that study day provides information on the number of days from the start of treatment (either active or sham) onwards, with the start of treatment being study day 1.

7.1.4 Days since Implant

The number of days since the implant will be calculated relative to the date of the implant, as follows:

$$\text{Days since implant} = \text{Assessment Date} - \text{Implant Date}$$

Note that days since implant provides information on the number of days since the implant, with the implant day being day 0.

7.1.5 Interim Analyses

Central monitoring reviews will be carried out by core study team members according to the Clinical Monitoring Plan. These in-stream reviews of data and reports will be used to identify any trends, patterns or safety signals, with a focus on key items identified in the clinical risk management plan.

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

A Data Safety Monitoring Board (DSMB) will evaluate safety data after the first implanted participant reaches Day 14 of Period 1 and will recommend either to continue implant procedures or other actions. Data provided to the DSMB will include: AEs, SAEs, ADEs, SADEs, treatment details, concomitant medication, vital signs, 12 Lead ECG, laboratory safety (haematology and clinical chemistry), protocol deviations, demography, and participant status. A full list of planned outputs will be provided in a separate document.

Safety data will be provided to MHRA after implant and the start of stimulation for the first participant.

7.1.6 Final Analyses

This study will include two reporting periods – the Primary reporting period (triggered by the last participant's last visit in Period 1 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. The database will be cleaned and locked and all data from Period 1 will be reported. Log forms (such as concomitant medications and AEs) will be as complete and clean as possible. Listings will include data from Period 2, where data cleaning and site monitoring will still be ongoing, so data from period 2 will not be considered final at this time.

The database will be cleaned and locked, all descriptive analyses will be performed and a CSR finalized.

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7.2 Analysis Populations

For purposes of analysis, the populations are defined in Table 4.

Table 4 Analysis populations

Population	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility, including those participants who signed the informed consent form (ICF) but didn't pass screening.	- Study Population - Safety
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.	- Study Population - Safety
Implanted	All enrolled participants in whom a device was implanted.	- Study Population - Safety
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.	- Study Population Period 1: - Safety - Efficacy - Biomarker
Long-Term Follow Up (LTFU)	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 Period 2, unless otherwise specified.	Period 2: - Safety - Efficacy - Biomarker

If all enrolled participants are successfully implanted, the Enrolled and Implanted populations will be equal; in this situation, the Implanted population will be labelled in data displays.

If all implanted participants receive at least one active stimulation during the treatment period, the Implanted and ITT populations will be equal; in this situation the ITT population will be labelled in data displays.

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7.3 Handling of Missing Data

All attempts will be made to limit the amount of missing data. Unless otherwise specified, no attempt will be made to impute missing data. The number of participants that contribute data to each analysis will be stated in the final report. In cases of participant withdrawal, data recorded from participants up to the time of withdrawal will be reported and analysed. Primary, secondary and exploratory endpoint data recorded from all participants will be included in the analyses, unless otherwise noted.

7.4 Derivation of Assessments

Derivation of the DAS28-CRP endpoint, as well as Tender/Painful Joint Count (28), Swollen Joint Count (28), Tender/Painful Joint Count (68), and Swollen Joint Count (66) is carried out within the database and is documented in the GAL1039 SRS.

7.4.1 Demographic Data

Age will be calculated by taking the difference between the year of birth and the year the informed consent was signed.

Where height is collected in inches, it is converted to centimeters using the following formula:

$$\text{Height (cm)} = \text{Height (inches)} * 2.54$$

Where weight is collected in pounds, it is converted to kilograms using the following formula:

$$\text{Weight (Kg)} = \text{Weight (pounds)} / 2.20462262$$

Duration of Rheumatoid Arthritis (years) is calculated as:

$$\text{Year of Screening} - \text{Year of Diagnosis of adult-onset Rheumatoid Arthritis (as defined by the 2010 ACR/EULAR classification criteria)}.$$

The listing of previous RA medications will display the number of years prior to implant that the medication was started and stopped:

$$\text{No. of years prior to implant that medication started} = \text{Year of implant} - \text{Year of start date}$$

$$\text{No. of years prior to implant that medication stopped} = \text{Year of implant} - \text{Year of stop date}$$

7.4.2 Allocating Data to a Study Period

Most study data will be collected on pages of the eCRF that are specific to study periods. However, unscheduled visits and log data (such as protocol deviations and adverse events) will need to be allocated to a specific study period for reporting purposes. The date of interest (e.g. the unscheduled visit date, PD date or AE start date) will be classified as shown in Table 5.

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Table 5 Study phase definitions

Study Phase	Definition
Pre-Surgery	Date of interest < Date of surgery
Pre-Treatment (Surgery and Recovery period)	Date of surgery ≤ Date of interest < Date of first active stimulation on Day 1
Open Label (Period 1)	Date of first active stimulation on Day 1 ≤ Date of interest ≤ P1 Exit date
LTFU (Period 2)	Date of interest > P1 Exit date

7.4.3 Adverse Events and Adverse Device Effects

Adverse events will be collected from Day -28 through to the Period 1, Day 84 assessment.

Adverse device effects will be collected from date of surgery through to the end of Period 2.

Serious adverse events and serious adverse device effects will be collected from the time of consent through to the end of Period 2.

All AEs will be classified using the current standard Medical Dictionary for Regulatory Activities (i.e. MedDRA version in use at the time of reporting (V24.0 or higher)), and grouped by System Organ Class (SOC) and Preferred Term (PT), unless otherwise stated. The MedDRA version will be detailed on every table that uses MedDRA.

The DSMB determined seriousness and relatedness will be used for applicable safety analyses. In cases where DSMB assessment has not yet been obtained for an event, the PI assessment of seriousness will be used. The same rule will be used for determining event relatedness. Both the investigator assessment of seriousness and device relatedness as well as DSMB assessment will be reported on relevant listings.

An adverse device effect is an adverse event that is considered to be related to the investigational medical device. An event will be considered 'related' if the relationship is reported as 'Probable' or 'Causal relationship'. Any AE that is related to the device will be reported as an ADE rather than an AE.

Disease Related Events (DRE's) are AEs that are considered expected from the underlying condition or those that are prevalent in the population being studied; therefore they would not typically be considered related to the study device or procedure (Protocol Section 10.3.4). These will be reported on the DRE form of the eCRF if the events are related to exacerbation of articular/peri-articular manifestations of RA (flare). Any AE that is recorded on the DRE form will be reported as a DRE rather than an AE.

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Events will be classified according to the time of occurrence relative to date of surgery and/or study treatment start date, as shown in Section 7.4.2, Table 5.

The duration of an event will be derived as: (Resolution Date – Onset Date) + 1.

7.4.4 Laboratory Safety Assessments

Laboratory safety assessments include data performed by the local hospital laboratory.

Lab normal ranges that will be used to identify if a particular parameter is outside of normal range can be found in “North Glasgow_Haematology User Manual Including Reference Ranges” for haematology parameters and “North Glasgow_Biochemistry User Manual Including Reference Ranges” for clinical chemistry parameters for Glasgow Site 001; “GAL1039 Site 003 AMC Lab Normals” will be used to identify lab normal ranges for AMC Site 003.

Where applicable, CTCAE grading will be provided (see table below for labs with CTCAE grading). CTCAE Version 5.0 grading will be used

(https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf; See Appendix 9.1 for details on where to find grading for each respective parameter). Only gradings which are based on numeric ranges will be provided. If an observed lab value does not meet any of the Grade 1 to 5 severity thresholds, it will be assumed to be normal and will not be flagged.

The laboratory assessments shown in Table 6, that are outside normal range will be presented.

Table 6 Laboratory Assessments and Parameters

Laboratory Assessments	Parameters			
Haematology	Platelet Count* RBC Count Haemoglobin* Haematocrit Erythrocyte Sedimentation Rate	<u>RBC Indices:</u> MCV MCH	<u>WBC count* with Differential:</u> Neutrophils* Lymphocytes* Monocytes Eosinophils Basophils	
Clinical Chemistry	Creatine* Glucose (non-fasting)* Albumin*	Potassium* Sodium* Chloride Urea	Aspartate aminotransferase (AST)* Alanine aminotransferase (ALT)* Alkaline phosphatase (AP) * C-Reactive Protein (CRP)	Total bilirubin* Direct bilirubin Total protein

*CTCAE grading available.

If a numeric laboratory value, has a non-detectable level reported in the database, then typically the numeric value is missing, and a character value starting with ‘<x’ or ‘>x’ is present. A numeric value will be derived using the number of decimal places in the observed character values, e.g.

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- 2 Decimal Places: '<x' becomes x-0.01
- 1 Decimal Place: '>x' becomes x+0.1
- 0 Decimal Places: '<x' becomes x-1

Autoimmune serology will be collected at Screening and presented in the summary of baseline characteristics as follows:

- Rheumatoid Factor:
 - ≤ 13.9 KIU/L = Negative (Glasgow Site 001 only)
 - > 13.9 KIU/L = Positive (Glasgow Site 001 only)
 - < 3.5 KU/L = Negative (AMC Site 003 only)
 - 3.5 to 5.0 KU/L = Equivocal (AMC Site 003 only)
 - > 5.0 KU/L = Positive (AMC Site 003 only)
- Anti-cyclic citrullinated peptide (anti-CCP):
 - < 7.0 U/mL = Negative
 - 7.0 to 10.0 U/mL = Equivocal
 - > 10.0 U/mL = Positive

7.4.5 Changes from Baseline

Changes from baseline will be calculated relative to Baseline (Day 1, Period 1) value of the study, unless otherwise noted.

- The calculation of absolute change from baseline: assessment value – baseline value.
- The calculation of percent change: $100 * (\text{assessment value} - \text{baseline value}) / \text{baseline value}$.

7.4.6 ACR Assessments

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 (PtGA)

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- Physician's Global Assessment of Arthritis (PhGA)
- CRP level (mg/L)
- Health Assessment Questionnaire – Disability Index (HAQ-DI)

Note that the details for the calculation of HAQ-DI are provided in Section 7.4.10.

The nACR improvement will be defined as the lowest value of the following (ACR 2007, Siegel & Zhen):

- % improvement of tender joint count
- % improvement of swollen joint count
- Median % improvement of Patient's Assessment of Arthritis Pain, PtGA, PhGA, CRP, and HAQ-DI.

If 'Tender Joint Count' or 'Swollen Joint Count' or 3 or more of the 5 remaining components are missing then nACR will be set to missing.

Additionally, ACR20/50/70 will be derived as supporting outcome measures. The American College of Rheumatology's definition for calculating improvement in RA (ACR20) is calculated as:

- $\geq 20\%$ improvement in tender joint counts AND
- $\geq 20\%$ improvement in swollen joint counts AND
- $\geq 20\%$ improvement in at least 3 of the 5 remaining ACR-core set measures specified above

The percent reduction will be calculated for each of the above components compared to Baseline (Day 1, Period 1). This calculation will be carried out by taking: $100 * (\text{Baseline value} - \text{assessment value}) / \text{Baseline value}$. For each ACR Assessment component noted above, greater numeric values are indicative of worse disease. Thus if the percent reduction is $\geq 20\%$ then there was a 20% improvement.

If the percent reduction is $\geq 20\%$ for both the 'Tender/Painful Joint Count' and 'Swollen Joint Count', and also for at least 3 out of 5 of the remaining components, then the subject will be considered a success for ACR20 (i.e. improvement in RA of at least 20%). Otherwise, the participant will be counted as a failure.

If 'Tender/Painful Joint Count' or 'Swollen Joint Count' or 3 or more of the 5 remaining components are missing then ACR20 will be set to missing.

Similarly, ACR50 and 70 are calculated with the respective percent improvement.

7.4.7 EULAR Response Rate

The EULAR modified response rate will be calculated based on the criteria in Table 6. For each assessment timepoint the criteria will be assessed using the Baseline (Day 1, Period 1) and assessment DAS-28(CRP) value at the timepoint of interest. If the baseline and/or visit assessment of the DAS28-CRP is missing, then the EULAR response rate will be set to missing.

Table 6 EULAR response criteria

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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

A good or moderate response equates to a EULAR Responder.

EULAR Remission is defined as a DAS28 (ESR) score <2.6.

The DAS28 (ESR and CRP) score can be interpreted as follows:

- <2.6: Disease remission
- 2.6 to 3.2: Low disease activity
- >3.2 to 5.1: Moderate disease activity
- >5.1: High disease activity

7.4.8 CDAI Assessments

The Clinical Disease Activity Index (CDAI) is a composite index for assessing disease activity (Aletaha, 2005). The CDAI is derived from:

- Tender/Painful Joint Count (28)
- Swollen Joint Count (28)
- Patient's Global Assessment of Arthritis (PtGA) (cm)
- Physician's Global Assessment of Arthritis (PhGA) (cm)

The formula for calculating the CDAI is as follows:

$$\text{CDAI} = (\text{tender28}) + (\text{swollen28}) + \text{PtGA (cm)} + \text{PhGA (cm)}$$

Note that the patient and physician global assessment scores are collected in the eCRF in millimeters, whereas the units for the calculation of CDAI are in centimeters. Therefore, these will be converted into cm by dividing by 10.

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A CDAI score of greater than 22.0 implies high disease severity, greater than 10.0 to 22.0 implies moderate disease severity, greater than 2.8 to 10.0 implies low disease severity, and 2.8 or less indicates remission.

If any of the components of the composite endpoint are missing, then CDAI will be set to missing.

7.4.9 SDAI Assessments

The Simple Disease Activity Index (SDAI) is a numerical sum of five measures (Smolen, 2003):

- Tender/Painful Joint Count (28)
- Swollen Joint Count (28)
- Patient's Global Assessment of Arthritis (PtGA) (cm)
- Physician's Global Assessment of Arthritis (PhGA) (cm)
- CRP level (mg/dL)

The formula for calculating the SDAI is as follows:

$$\text{SDAI} = (\text{tender28}) + (\text{swollen28}) + \text{PtGA (cm)} + \text{PhGA (cm)} + \text{CRP (mg/dL)}$$

Note that the patient and physician global assessment scores are collected in the eCRF in millimeters, whereas the units for the calculation of SDAI are in centimeters. Therefore, these will be converted from mm into cm by dividing by 10.

Note that the CRP values are stored in the lab dataset in mg/L whereas the units for the calculation of SDAI are in mg/dL. Therefore, the CRP values will be converted from mg/L into mg/dL by dividing by 10.

A SDAI score of greater than 26.0 implies high disease severity, greater than 11.0 to 26.0 implies moderate disease severity, greater than 3.3 to 11.0 implies low disease severity, and 3.3 or less indicates remission.

If any of the components of the composite endpoint are missing, then SDAI will be set to missing.

7.4.10 HAQ-DI

The Disability Index of the Stanford Health Assessment Questionnaire (HAQ-DI) will be used to assess functional status of the participant (Wolfe, 1989; Wolfe et al, 1994). This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks in eight functional areas, from which a single disability index is calculated: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. There are two to three questions for each function area.

Scoring within each section is from 0 (without any difficulty) to 3 (unable to do). For each section the score given to that section is the worst score within the section, i.e. if one question is scored 1 and another 2, then the score for the section is 2. In addition, if an aide or device is used or if help is required

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from another individual, then the minimum score for that section is 2. If the section score is already 2 or more then no modification is made.

The scores from each of the eight sections are summed and divided by eight. The result is the disability index (DI). Total score ranges from 0 to 3.

In the event that one section is not completed by a participant then the summed score would be divided by seven. In the event that two or more sections are not completed by a participant, the score will be set to missing.

Source for scoring:

https://www.niehs.nih.gov/research/resources/assets/docs/haq_instructions_508.pdf.

7.4.11 RAID

A RAID value will be calculated using the participant completed Rheumatoid Arthritis Impact Of Disease (RAID) questionnaire.

The RAID is calculated based on seven numerical rating scales (NRS) questions, each weighted differently. Each NRS is assessed as a number between 0 and 10. The seven NRS correspond to pain, function, fatigue, sleep, emotional well-being, physical well-being, and coping/self-efficacy.

Calculation of RAID final value = (pain NRS value (range 0-10) x 0.21) +
(function NRS value (range 0-10) x 0.16) +
(fatigue NRS value (range 0-10) x 0.15) +
(phys well being NRS value (range 0- 10) x 0.12) +
(sleep NRS value (range 0-10) x 0.12) +
(emotional well being NRS value (range 0-10) x 0.12) +
(coping NRS value (range 0-10) x 0.12).

The range of the final RAID value is 0-10 where higher figures indicate worse status.

If one of the seven NRS values is missing, the imputation is as follows:

- calculate the mean value of the six other (non-missing) NRS (range, 0-10)
- impute this value for the missing NRS
- Then, calculate the RAID as explained above.

If two or more of the NRS are missing, the RAID is considered as missing value (no imputation).

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Source for scoring: http://oml.eular.org/sysModules/obxOml/docs/ID_6/raid_en_GB.pdf

7.4.12 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.

A dataset with the response to each of the 36 questions at each visit will be exported into comma delimited (CSV) file and read into Quality Metric PRO CoRE Smart Measurement System (version 2.0 or later). The scoring software will create the eight domain scales (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, Mental Health), and also the component scores (physical and mental). The scores obtained from the scoring software will be the basis for any analyses of SF-36.

7.5 IPG Data

Implantable Pulse Generator (IPG) data for each participant is downloaded directly from the device on a regular basis by the field clinical engineers (FCE) at the site. The data is downloaded in a large csv file and is manipulated into smaller spreadsheets to make the data usable. Due to the device storage capacity, earlier records are overwritten and so the data has to be continually saved and concatenated for each participant.

7.5.1 Common variables across spreadsheets

Days since implant will be calculated as per Section 7.1.4 and will represent the number of whole days since the implant.

Duration is calculated as the number of days since the implant and is stored to multiple decimal places:

Duration = date/time variable of interest – date/start time of surgery (time of first incision)*

* Note that date/start time of surgery are taken from the eCRF.

7.5.2 Battery Level

Data is selected when the log type equals “Battery check”, “Charging session started” and “Charging session completed”. Variables will include:

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- Participant ID
- Date/time
- Duration: see Section 7.5.1
- Days since implant: see Section 7.5.1
- Battery Level (mV): Numeric value from 'Description' variable
- Log type: Source log type

7.5.3 Therapy Delivery All Data

Data is selected when the log type equals "Therapy Delivery". Variables will include:

- Participant ID
- Date
- Days since implant: see Section 7.5.1
- Start Time: Time when Description column includes "Started"
- Completion Time: Time when Description column includes "Completed"
- Therapy Number: Numeric value extracted from Description column
- Type (Automatic/Manual): Text extracted from Description column
- Duration (sec): Numeric value extracted from Description column

7.5.4 Therapy Delivery Summary

Data is selected when the log type equals "Therapy Delivery". Variables will include:

- Participant ID
- Date
- Days since implant: see Section 7.5.1
- Number of manual therapies delivered: Count of manual therapies on specified date
- Number of automatic therapies delivered: Count of automatic therapies on specified date
- Total number of therapies delivered: Sum of manual and automatic counts on specified date

7.5.5 Therapy Adjustment

Data is selected when the log type equals "Therapy Adjustment". Variables will include:

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- Participant ID
- Date
- Time
- Days since implant: see Section 7.5.1
- Log number
- For each distinct log number, the following variables will be included:
- Pulse Amplitude (mA): Numeric value extracted from Description column
- Pulse width (μ s): Numeric value extracted from Description column
- Pulse Rate (Hz): Numeric value extracted from Description column
- Duration (sec): Numeric value extracted from Description column
- Ramp (sec): Numeric value extracted from Description column
- Micoburst Period (sec): Numeric value extracted from Description column
- Micoburst Active Period (sec): Numeric value extracted from Description column
- Electrode Configuration: Text extracted from Description column

7.5.6 Impedance

Data is selected when the log type equals “Impedance measurement”. Variables will include:

- Participant ID
- Date/time variable
- Days since implant: see Section 7.5.1
- Duration: see Section 7.5.1
- C2D_impedance_Ohm: Numeric value extracted from Description column when text includes “Case to Distal”
- C2P_Impedance_Ohm: Numeric value extracted from Description column when text includes “Case to Proximal”
- D2P_Impedance_Ohm: Numeric value extracted from Description column when text includes “Distal to Proximal”

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- Calculated ratio: Maximum value of the ratio for C2D/C2P and the ratio for C2P/C2D

7.5.7 Battery Charging

Data is selected when the log type equals “Charging”, “Charging session completed” or “Charging session started”. Variables will include:

- Participant ID
- Date variable
- Days since implant: see Section 7.5.1
- Total time spent charging on day (minutes): a sum of time between “Charging session started” and “Charging session completed” for a given day, based on days since implant above.
- If there is a missing record for ‘charging session started’ and it was the only charging session recorded that day, Time will be recorded as zero. If there were other charging sessions recorded that day, Time will be the sum for the sessions that have complete start/stop information
- If there is a missing record for ‘charging session complete’ and it was the only charging session recorded that day, Time will be recorded as missing. If there were other charging sessions recorded that day, Time will be the sum for the sessions that have complete start/stop information
- Number of charging sessions on day: a sum of total times a charging session was started/stopped for a given day, based on days since implant above
- Extreme value (>150 minutes): ‘Yes’ if time spent charging on day >150

7.5.8 Pre Post Impedance Distal to Proximal (D2P)

Data is selected when the log type equals “Impedance measurement” and the Description column contains “Automatic, Distal to Proximal” or log type equals “Therapy delivery” and the Description column does not include “manual”. Variables will include:

- Participant ID
- Date
- Days since implant: see Section 7.5.1
- Duration: see Section 7.5.1

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- Stim number: pulled from columns where log type is “Therapy delivery”, and includes the number that occurs after the pound (#) sign.
- Pre: Numeric value of impedance extracted from Description column for the record immediately preceding the therapy delivery start date/time of a given stim number
- Post: Numeric value of impedance extracted from Description column for the record immediately after the therapy delivery completion date/time of a given stim number
- % Difference: Calculated as $((\text{Post}-\text{Pre})/\text{Pre}) * 100$

7.5.9 Pre Post Impedance Case to Distal (C2D)

Data is selected when the log type equals “Impedance measurement” and the Description column contains “Automatic, Case to Distal” or log type equals “Therapy delivery” and the Description column does not include “manual”. Variables will include:

- Participant ID
- Date
- Days since implant: see Section 7.5.1
- Duration: see Section 7.5.1
- Stim number: pulled from columns where log type is “Therapy delivery”, and includes the number that occurs after the pound (#) sign.
- Pre: Numeric value of impedance extracted from Description column for the record immediately preceding the therapy delivery start date/time of a given stim number
- Post: Numeric value of impedance extracted from Description column for the record immediately after the therapy delivery completion date/time of a given stim number
- % Difference: Calculated as $((\text{Post}-\text{Pre})/\text{Pre}) * 100$

7.5.10 Pre Post Impedance Case to Proximal (C2P)

Data is selected when the log type equals “Impedance measurement” and the Description column contains “Automatic, Case to Proximal” or log type equals “Therapy delivery” and the Description column does not include “manual”. Variables will include:

- Participant ID
- Date
- Days since implant: see Section 7.5.1

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- Duration: see Section 7.5.1
- Stim number: pulled from columns where log type is “Therapy delivery”, and includes the number that occurs after the pound (#) sign.
- Pre: Numeric value of impedance extracted from Description column for the record immediately preceding the therapy delivery start date/time of a given stim number
- Post: Numeric value of impedance extracted from Description column for the record immediately after the therapy delivery completion date/time of a given stim number
- % Difference: Calculated as $((\text{Post}-\text{Pre})/\text{Pre}) * 100$

7.5.11 Therapy Adjustment with Dose Escalation

Data is selected when the log type equals “Therapy Adjustment” and the Description column contains “Pulse Amplitude:”, “Pulse width:”, “Pulse rate:”, “Duration:”, “Ramp:”, “Microburst period:”, “Microburst active period:”, or “Electrode configuration”. Data will be transposed by Participant ID, log number, date, time, days since implant and duration (see Section 7.5.1). From each unique ID, date and time record, stimulation number is assigned starting at #1 for the first time record on that date, and increasing in number for each time, until the start of the next date. This data then merges with the dose escalation ramp-up visit data from the EDC by ID, date and stimulation number, with a flag for whether the record is in both datasets. Flagged data, or the last record on a given day (i.e. days since implant) is selected and merged with a temporary dataset described below by day.

A temporary dataset is created where there is a row for each possible day since implant through the last day data was observed on the plot. IPG data when the log type equals “Therapy Adjustment” is merged with this temporary dataset by ID and days since implant to define whether any therapy was delivered on each possible day. Once this dataset is combined with the final dataset outlined in the previous paragraph, pulse amplitude is defined, and any cases where no therapy was delivered on a date will set amplitude value to zero.

Variables in the listing will include:

- Participant ID
- Log number
- Date
- Time
- Days since implant: see Section 7.5.1
- Pulse Amplitude

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- Pulse Width
- Pulse Rate
- Duration (seconds)
- Ramp (seconds)
- Microburst Period (seconds)
- Microburst Active Period (seconds)
- Electrode Configuration
- Analysis Visit: from dose escalation ramp-up visit data in the EDC
- Did the participant indicate that they felt any sensation (including discomfort) potentially related to stimulation application during this stimulation? : from dose escalation ramp-up visit data in the EDC
- Did the participant experience any discomfort with this sensation: from dose escalation ramp-up visit data in the EDC
- Rate level of discomfort: from dose escalation ramp-up visit data in the EDC

Stim number: defined based on unique date and time for a delivered therapy, and also directly from dose escalation ramp-up visit data in the EDC

8 Analysis of Study Population

Study Population outputs will only be presented for Period 1 unless otherwise specified.

8.1 Subject Disposition

The number of subjects in each analysis population will be presented for relevant populations in both Periods 1 and 2.

The reasons for screen failure will be summarized.

The number of subjects who are enrolled, and number completing a visit will be summarized for each protocol-required visit for both Periods 1 and 2. In addition, the number of subjects who complete Periods 1 and 2 or discontinue early will be summarized by reason for both Periods 1 and 2.

Listings of study completions/withdrawals, and revision surgeries/explants will also be provided for both Periods 1 and 2.

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8.2 Demographics and Baseline Characteristics

Descriptive statistics will be presented for all clinically relevant baseline demographic characteristics and baseline efficacy measures.

The number of participants with clinically significant medical history will be presented.

Listings of participant demographics, medical history, screening tests, and imaging (CT-angiography, abdominal Xray, and Ultrasound) will also be provided. A listing of Ultrasound scans will also be provided for Period 2.

8.3 Surgical Procedure and Recovery

Listings of surgical data, device components (implanted device components, external device components, and external device accessories), and post-operative checks will be provided.

8.4 Medications

A summary of previous RA medication therapy will be presented.

Listings will be provided for the following: previous RA medication therapy, perioperative (during surgery) medications, and all reported concomitant medications (post-surgery).

A listing of all reported concomitant medications will also be provided for Period 2. As per the Protocol, this should be limited to disease-related, SAE-related and any immuno-modifying medications.

8.5 Treatment Details

Listings of device check data, programming and stimulation details, ramp-up dose escalation, participants stopping therapy and unscheduled programming visits will be provided for Periods 1 and 2.

8.6 Protocol Deviations

Protocol deviations during Period 1 will be summarized overall and by type/category with deviations counts and number of participants with at least one deviation. They will be presented overall and by minor/major classification.

A listing of protocol deviations will also be provided for Periods 1 and 2.

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9 Analysis of Study Endpoints

9.1 Statistical Hypotheses

No single hypothesis was utilised to drive a sample size for this study because it is an early feasibility study.

9.2 Primary Endpoints

9.2.1 Adverse Events

Period 1: Summaries of AEs, SAEs, ADEs, and SADEs that started pre-surgery and those that started pre-treatment (during surgery/recovery period) will be provided by system organ class and preferred term.

Summaries of AEs, SAEs, ADEs, and SADEs that started during Period 1 will be provided by system organ class and preferred term. DSMB assessment will be used for event seriousness and relatedness. In cases where DSMB assessment has not yet been obtained for an event, the PI assessment of seriousness will be used. The same rule will be used for determining event relatedness. Individual subject listings of AEs, SAEs, ADEs, SADEs, disease related events (DREs) and device events (DEs) will also be provided. Both DSMB and PI assessments of seriousness and study device relatedness will be provided in listings. A listing of participant deaths will also be provided. Period 2: Summaries of SAEs, ADEs, and SADEs that started during Period 2 will be provided by system organ class and preferred term. DSMB assessment will be used for event seriousness and relatedness. In cases where DSMB assessment has not yet been obtained for an event, the PI assessment of seriousness will be used. The same rule will be used for determining event relatedness.

Individual subject listings of SAEs, ADEs, SADEs, DREs and DEs that started during Period 2 will also be provided. Both DSMB and PI assessments of seriousness and study device relatedness will be provided in listings. A listing of participant deaths during Period 2 will also be provided.

9.2.2 Laboratory data

Clinical chemistry and haematology data will be summarized at each relevant assessment timepoint (screening, Day 1 pre-stimulation, Day 7, Day 14, Day 28, Day 56 and Day 84) utilizing descriptive statistics. The change from Baseline will also be summarized.

A Figure to display CRP values over time for each participant will be provided.

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Figures for clinical chemistry and haematology pre-specified parameters of interest will be presented. This following are the pre-specified parameters of interest:

- Clinical Chemistry
 - Sodium (MMOL/L)
 - Potassium (MMOL/L)
 - Phosphorus (or Phosphate) - inorganic (MMOL/L)
 - Bicarbonate (MMOL/L)
 - Chloride (MMOL/L) - split by age 1-90/91+
 - Calcium (MMOL/L) - split by age 18-59/60-90/91+
 - ALT (or ALAT): Alanine Amino Transferase (U/L) – split by Male/Female
 - AST (or ASAT): Aspartate Amino Transferase (U/L) – split by Male/Female
 - Creatinine (UMOL/L) – split by Male/Female
 - AMC Site 003 further split by age 19-50/51-65/66-80/81+
 - High Sensitivity C Reactive Protein
 - Total Bilirubin
- Haematology
 - White blood cell count (GI/L)
 - Platelet count (GI/L)
 - Red blood count (TI/L) – split by Male 18-64/Male 65+/Female 18-64/Female 65+
 - AMC Site 003 split only by Male/Female
 - Haemoglobin (G/L) - split by Male 18-64/Male 65+/Female 18-64/Female 65+
 - AMC Site 003 split only by Male/Female
 - Haematocrit - split by Male 18-64/Male 65+/Female 18-64/Female 65+
 - AMC Site 003 split only by Male/Female
 - Erythrocyte sedimentation rate – split by Male ≤50/Male > 50/Female ≤50/Female > 50

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Shift change from baseline tables will be created, using laboratory normal ranges to classify as above or below normal limit.

Listings of haematology and clinical chemistry data will be provided for all participants. Additional listings of haematology and clinical chemistry data for relevant laboratory parameters will be provided to display any assessment with a CTCAE grading of 3 or 4.

9.2.3 Vital Signs data

Period 1: Blood pressure, heart rate, respiratory rate, and body temperature data will be summarized at each relevant assessment timepoint (screening, Day -18, Baseline, Day 4, Day 7, Day 14, Day 28, Day 42, Day 56, Day 70 and Day 84) utilizing descriptive statistics. The change from Baseline (Day 1, Period 1) and percentage change from Baseline (Day 1, Period 1) will also be summarized.

A figure will also be provided, where data for each participant is plotted across each assessment timepoint for all listed parameters.

Listings of vital sign data and physical exam data collected during Screening and Period 1 will also be provided.

Period 2: Blood pressure, heart rate, respiratory rate, and body temperature data will be summarized at each relevant assessment timepoint (Periods 1 and 2) utilizing descriptive statistics. The change from Baseline (Day 1, Period 1) and percentage change from Baseline (Day 1, Period 1) will also be summarized.

A figure will also be provided, where data for each participant is plotted across each assessment timepoint (Periods 1 and 2) for all listed parameters.

Listings of vital sign data and physical exam data collected during Period 2 will also be provided.

9.2.4 ECG data

Period 1: Heart rate, PR, QRS, QT, and QTc intervals collected by ECG at each relevant timepoint (screening, Baseline, Day 4, Day 7, Day 14, Day 28, Day 42, Day 56, Day 70 and Day 84) will be summarized using descriptive statistics. The change from Baseline (Day 1, Period 1) and percentage change from Baseline (Day 1, Period 1) will also be summarized.

A listing of abnormalities identified by ECG during Screening and Period 1 will be provided.

Period 2: Heart rate, PR, QRS, QT, and QTc intervals collected by ECG at each relevant timepoint (Periods 1 and 2) will be summarized using descriptive statistics. The change from Baseline (Day 1, Period 1) and percentage change from Baseline (Day 1, Period 1) will also be summarized.

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A listing of abnormalities identified by ECG during Period 2 will be provided.

9.3 Secondary Endpoints

The secondary endpoints below will be reported in listing format for both Periods 1 and 2:

- Patient and clinicians' feedback on the use of CP, PR, Charger, Belt and Adhesive patch using sponsor-developed questionnaires.
- Participant's feedback using a sponsor developed questionnaire.
- Tabulation of device deficiencies
 - The events provided for this listing will be the device events reported. A subset of those events are 'device deficiencies', for which additional information will be provided by the quality team.

9.3.1 IPG and Device Testing

A listing of device testing data will be provided.

The following exploratory endpoints will be provided in listing format:

- Impedance as measured by the IPG before and after Intraoperative stimulation
- Measurement of the Heart Rate (HR) before, during, and after Intraoperative stimulation
- Measurement of the Systemic Blood Pressure (SBP) before, during, and after Intraoperative stimulation

Intraoperative cardiovascular data (HR and SBP) will also be displayed separately in graphical format for participants with BP cuff used and participants with IA line placed.

Figures will also be produced for each participant separately using the IPG data described in Section 7.9. These figures will present data over time, using days since implant on the x-axis. Vertical lines will represent the dates that the individual participant leaves each period (taken from the Period Exit forms in the eCRF).

Figure 1 will present the battery level (mV) over time.

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Figure 2A will present the impedance level (Ohms) over time on the day of implant or before, for Case to Distal, Case to Proximal and Distal to Proximal.

Figure 2B will present the impedance level (Ohms) over time after the day of implant, for Case to Distal, Case to Proximal and Distal to Proximal.

Figure 3 will present the total time spent charging on each day (minutes).

Figure 4 will present the impedance percentage change from pre to post therapy delivery over time, Distal to Proximal.

Figure 5 will present the pre-stimulation impedance values over time, Distal to Proximal.

Figure 6 will present the post-stimulation impedance values over time, Distal to Proximal.

Figure 7A will present the total number of daily therapies (manual plus automatic) over time. Note the following:

- Every day that the participant is receiving a therapy (stimulation ON, or OFF) there should be at least one therapy delivered. If any day is missing from the log, the total number of daily therapies will be included as zero.
- Whilst the participant device is switched off, i.e. the device is in hibernation mode, the total number of daily therapies will be included as zero.

Figure 7B will present the number of daily manual therapies over time in one colour, and the number of daily automatic therapies over time in another colour, as described above. The number of manual therapies will only be presented when it is greater than zero.

Figure 8 will present the pulse amplitude (mA) that the participant is receiving over time. Note the following:

- The latest pulse amplitude from each day will be used. On ramp up days, this will represent the final amplitude of the day, i.e. the device will be programmed to this amplitude until the next adjustment.
- On days where the total number of daily therapies is zero, the amplitude should be set to zero, as no therapies have been delivered that day. On days where the total number of daily therapies is greater than zero, the amplitude is equal to the final amplitude of the day, as described above.

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Figure 9 will present the pulse amplitude (mA) that the participant is receiving over time. Note the following:

- For dates associated with a ramp-up visit, the level of amplitude for each stimulation on that day will be included. For all other dates the latest pulse amplitude from each day will be used.
- On days where the total number of daily therapies is zero, the amplitude should be set to zero, as no therapies have been delivered that day. On days where the total number of daily therapies is greater than zero, the amplitude is equal to the final amplitude of the day, as described above.
- For ramp-up visits, EDC dose escalation sensation data will be combined with IPG device data by date and stimulation number. For each stimulation on a given dose escalation visit date the level of discomfort reported for that stimulation will be indicated by having varying colors for the possible levels of discomfort: no sensation, none, mild, moderate, and severe.

Figure 10 will present the pulse amplitude (mA) that the participant is receiving through Period 1. Data presented will be the same as that provided in Figure 9, but is limited to data through Period 1.

9.3.2 Evaluating usability of the device

Data from the sponsor-developed questionnaires for physician feedback on the use of the CP, PR, Charger, Belt and Adhesive patch will be provided in a listing format. In Period 1, data is only collected within a month of the site's first participant reaching Day 28. A listing of site comments will also be provided.

Data from the sponsor-developed questionnaire for participants feedback will be provided in the following listings for Day 14, Day 28, Day 56 and Day 84:

- Using Patient Remote
- Charging Accessories and the Implant
- Implant Battery Status and Charging
- Instructions for Use
- Stopping Therapy

The following key questions of interest will be summarized in histograms over time for Period 1 and 2 (all treatment groups combined):

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- How often did you delay your therapy?
- How easy did you find charging your implant (including alignment of IPG charger over your implant)?
- Which method did you prefer to hold the IPG charger in place during charging?
 - How easy did you find using the Charging Belt with the IPG charger for charging your implant?
 - How easy did you find using the adhesive patch with the IPG charger for charging your implant?
- How often did you check your battery status?
- Did you check your battery status before charging your implant?
- How often have you charged your implant?
- How long was a typical charging session for your implant?
- Did you fully charge your implant at each charging session, so that battery status = High?
- Did you stop your therapy?

9.3.3 Device Events and Deficiencies

Device event data will be based on data collected in the EDC, merged with Grand Avenue Software (GAS) complaint data from the quality system. The data from GAS provided DE investigation information per the Galvani team. Data is combined using the participant ID and complaint number. A summary of device events that occurred from the time of surgery onwards throughout the study, regardless of Period, will be produced. The summary will display the total number of device events split by category (i.e. primary product involved) and overall, plus how many of them had adverse events potentially associated with them and how many of them could have led to a serious adverse event if suitable action had not been taken or intervention had not been made or if circumstances had been less fortunate. Total reported device events will also be reported which will be based on the number of device event forms in the EDC. Its possible that there will be more than one product or device component associated with a single device event reported in the EDC so the sum of events across product categories may be greater than the total number of reported device events.

A listing of all device events will also be provided for all implanted participants. A subset of these device events are 'device deficiencies', for which additional information will be provided by the quality team.

Information included in the listing that are not collected in the EDC include:

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- Complaint Closed Date
- Complaint Classification
- Primary Product Involved
- Investigation Results
- Root Cause
- End Effect (Harm) and Severity
- Clinical Resolution

9.4 Exploratory Endpoints

9.4.1 Period 1:

The following exploratory endpoints will be listed and summarized using descriptive statistics. Figures will also be generated to view the endpoints over time.

- Absolute change from baseline (Day 1, Period 1) in SDAI at Day 14, 28, 42, 56, 70 and 84
- Absolute change from baseline (Day 1, Period 1) in DAS28-CRP at Day 14, 28, 42, 56, 70 and 84
- Absolute change from baseline (Day 1, Period 1) in CDAI at Day 14, 28, 42, 56, 70 and 84
- nACR improvement, defined as the lowest value of (% improvement of tender joint, swollen joint, median % improvement in the 5 remaining measures), at Day 84
- Proportion of participants achieving a moderate/good EULAR response at Day 84
- Absolute change from baseline (Day 1, Period 1) in HAQ-DI score at Day 14, 28, 56 and 84
- Absolute change from baseline (Day 1, Period 1) in physical and mental component scores and domain scores of SF-36 at Day 14, 28, 56 and 84
- Absolute change from baseline (Day 1, Period 1) in quality of life as measured by RAID at Day 14, 28, 56 and 84

The following exploratory endpoints will be reported in listing format:

- Impedance as measured by the IPG before and after intraoperative stimulation.
- Measurement of the heart rate (HR) before, during and after intraoperative stimulation along with change from Baseline and percent change from Baseline.
- Measurement of the systolic blood pressure (SBP) before, during and after intraoperative stimulation along with change from Baseline and percent change from Baseline.

Intraoperative cardiovascular data (HR and SBP) will also be displayed in graphical format.

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9.4.2 Period 2:

The following exploratory endpoints will be listed and summarized using descriptive statistics:

- Number of participants achieving DAS28-CRP ≤ 2.6 at Month 3 of Period 2
- Number of participants achieving DAS28-CRP ≤ 2.6 at Month 6 of Period 2
- Absolute change from baseline (Day 1, Period 1) in SDAI at Period 1 timepoints (Day 14, 28, 42, 56 and 84) and Period 2 timepoints (Months 1 to 60 as per Protocol schedule of events)
- Absolute change from baseline (Day 1, Period 1) in DAS28-CRP at Period 1 timepoints (Day 14, 28, 42, 56 and 84) and Period 2 timepoints (Months 1 to 60 as per Protocol schedule of events)
- Absolute change from baseline (Day 1, Period 1) in CDAI at Period 1 timepoints (Day 14, 28, 42, 56 and 84) and Period 2 timepoints (Months 1 to 60 as per Protocol schedule of events)
- nACR improvement, defined as the lowest value of (% improvement of tender joint, swollen joint, median % improvement in the 5 remaining measures), at Period 2 timepoints (Months 1 to 60 as per Protocol schedule of events) compared to baseline (Day 1, Period 1)
- Proportion of participants achieving a moderate/good EULAR response at Period 1 timepoint (Day 84) and Period 2 timepoint (Month 60)
- Absolute change from baseline (Day 1, Period 1) in HAQ-DI score at Period 1 timepoints (Day 14, 28, 42, 56 and 84) and Period 2 timepoints (Months 1 to 60 as per Protocol schedule of events)
- Absolute change from baseline (Day 1, Period 1) in physical and mental component scores and domain scores of SF-36 at Period 1 timepoints (Day 14, 28, 42, 56 and 84) and Period 2 timepoints (Months 1 to 60 as per Protocol schedule of events)
- Absolute change from baseline (Day 1, Period 1) in quality of life as measured by RAID at Period 1 timepoints (Day 14, 28, 42, 56 and 84) and Period 2 timepoints (Months 1 to 60 as per Protocol schedule of events)

9.4.3 Periods 1 & 2:

For composite endpoints each component of the assessment will also be reported. The absolute changes from baseline (Day 1, Period 1) at each assessment time point over time will be reported.

A Figure will be provided to display DAS28-CRP values over time for each subject.

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9.5 Supporting Endpoints

9.5.1 nACR

The ACR20, ACR50, and ACR70 will be derived for each participant and provided in listing format as a supporting outcome measure, alongside ACR-N, for Periods 1 and 2.

9.5.2 Biomarkers

The following continuous biomarker endpoints will be summarized using descriptive statistics. Absolute values and the percentage change from baseline will be presented.

- levels of LPS stimulated whole blood assay secondary objective assessments at protocol specified visits
- levels of LPS stimulated whole blood assay exploratory assessments at protocol specified visits
- levels of LPS stimulated whole blood assay post-hoc assessments at protocol specified visits

Figures will also be provided for each parameter above to display the mean percentage change from baseline ($\pm$ Standard Error) over time. Figures plotting the mean percentage change from baseline ($\pm$ standard deviation) along with individual participant percentage change data for each above measure. Figures with individual participant data will be plotted over time for both the absolute value and percentage change from baseline.

For the LPS stimulated whole blood assay exploratory assessments, additional figures will be created where the mean change from baseline ($\pm$ standard deviation) in DAS28-CRP will be plotted on the same plot as each measure (mean of absolute value $\pm$ standard deviation). All relevant visits for biomarker data and DAS data will be displayed on the x-axis. For each participant a similar plot will be produced for each measure, plotting their change from baseline in DAS28-CRP and observed value for each biomarker measure. A bar plot for each measure of the mean percent change from baseline ($\pm$ standard deviation) will be provided, with an overlaid scatter plot of each participants percent change from baseline to each respective visit.

Two additional figures for all measures will be provided for Sentinel participants through Day 84. In the first figure individual participant percentage change data for each measure will be plotted. The color of the lines for each participant will be dependent on whether that participant was a responder at their Day 84 visit or not. A participant is considered to be a DAS28 (CRP) responder if they have a reduction from baseline of >1.2 . The second figure will plot each participants absolute value at baseline, along with the mean at baseline by whether they were responders at Day 84.

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A listing of LPS-inducible release of cytokines in whole blood assay measured in the TruCulture OptiMAP panel will also be provided.

10 Changes from Planned Analyses

Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amended Statistical Analysis Plan and approved prior to the analysis when possible.

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11 References

Aletaha, Daniel, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther*. 2005; 7(4): R796–R806.

American College Of Rheumatology Committee To Reevaluate Improvement Criteria [ACR]. A Proposed Revision to the ACR20: The Hybrid Measure of American College of Rheumatology Response. *Arthritis & Rheumatism (Arthritis Care & Research)* 2007; 57(2):193-202.

Siegel, Jeffrey N and Zhen, Bo-Guang. Use of the American College of Rheumatology N (nACR) index of improvement in rheumatoid arthritis: argument in favor. *Arthritis Rheum*. 2005; 52(6):1637-41.

Smolen, J. S., et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology* 2003; 42:244–257.

Wolfe F. A brief clinical health assessment instrument: CLINHAQ. *Arthritis Rheum*. 1989; 32 (suppl): S9.

Wolfe F, et al. Rheumatoid arthritis: pathogenesis, assessment, outcome and treatment. *New York: Marcel Dekker*, 1994: 463-514.

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12 Appendices

12.1CTCAE Version 5.0 Grading for Applicable Parameters

<u>Laboratory Parameter</u>	<u>Page #</u>	<u>CTCAE Term(s)</u>
Platelet Count	83	Platelet count decreased
Hemoglobin	2	Anemia
	82	Hemoglobin increased
WBC Count	84	White blood cell decreased
Neutrophils	83	Neutrophil count decreased
Lymphocytes	83	Lymphocyte count decreased
	83	Lymphocyte count increased
Potassium	86	Hyperkalemia
	87	Hypokalemia
Sodium	86	Hypernatremia
	87	Hyponatremia
AST	79	Aspartate aminotransferase increased
ALT	79	Alanine aminotransferase increased
AP	79	Alkaline phosphatase increased
Creatinine	81	Creatinine increased
Glucose	87	Hypoglycemia
Tbili	79	Blood bilirubin increased
Albumin	87	Hypoalbuminemia