A MULTIPART EXPLORATORY STUDY TO EVALUATE SPLENIC NERVE STIMULATION IN PATIENTS WITH RHEUMATOID ARTHRITIS

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The Galvani Splenic Neuromodulation System consists of a lead, rechargeable implantable pulse generator, external components and accessories. The system is designed to deliver electrical stimulation to the splenic NVB in patients with moderate to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON52223

Source
ToetsingOnline

Brief title
Splenic nerve stimulation in patients with rheumatoid arthritis

Condition

- Autoimmune disorders
- Joint disorders

Synonym
rheumatoid arthritis; Arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Galvani Bioelectronics
Source(s) of monetary or material Support: Galvani Bioelectronics

Intervention

Keyword: Immunomodulation, Implantable device, Neuromodulation, Rheumatoid arthritis

Outcome measures

Primary outcome

The primary objective and associated endpoints for each period of this

multipart study are:

1. To evaluate the safety and tolerability of the Galvani splenic

neuromodulation system and 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 ECG monitoring.

Secondary outcome

Secondary objectives and endpoints are:

1. For the Randomized Control Trial (Period 1) - to evaluate the effect of

splenic NVB stimulation on the clinical signs and symptoms of RA as assessed by:

a. Change from baseline in the 28 Joint Disease Activity Score DAS28 at week 12 (end of Period 1).

2. For the Randomized Control Trial and Open Label periods (Periods 1-2) - to evaluate the effect of splenic NVB stimulation on the change in pharmacodynamic and response biomarkers as assessed by:

a. Changes from baseline in the levels of LPS-inducible release of TNFα, IL-6, IL-8, and IL-17 in whole blood assay at assessment timepoints.

3. Throughout each period of this multipart study:

a. to evaluate the effect of splenic NVB stimulation on the clinical signs and symptoms of RA as assessed by:

i. change from baseline in DAS28 at assessment timepoints

b. to evaluate the effect of splenic NVB stimulation on Patient Reported Outcomes as assessed by:

i. change from baseline in HAQ-DI score at assessment timepoints

ii. change from baseline in physical and mental component scores as well as domain scores of SF-36 at assessment timepoints.

c. to evaluate the usability of the clinician and patient external devices and accessories as assessed by participants* and clinicians* feedback on the use of CP, PR, IPG Charger, Belt and Adhesive patch using sponsor-developed questionnaires.

d. to evaluate the participants* perception of therapy and sensation as assessed by participants* feedback using a sponsor-developed questionnaire.

e. to evaluate the device performance as assessed by the tabulation of device deficiencies.

Additional secondary objectives and endpoints specific to the Open Label Treatment phase (Period 2) are:

1. For the cohort of participants on active stimulation during the RCT Phase (i.e., Period 1) who achieve a clinical response (i.e.: > 1.2 units of improvement on DAS28) at week 12: to determine whether this response can be sustained and/or extended upon 12 additional weeks of active stimulation as assessed by:

a. Change from week 12 to week 24 in DAS28.

b. Achievement of DAS28 score of < 2.6 at week 24.

2. For the cohort of participants on sham stimulation during the RCT Phase and for participants who failed to achieve an adequate clinical response on active stimulation during the RCT Phase at week 12: to provide active treatment with baricitinib - an approved therapy for this patient population - and determine response to this therapy as assessed by:

a. Change from week 12 to week 24 in DAS28.

b. Achievement of clinical response (> 1.2 units of improvement on DAS28) at week 24 vs. week 12.

c. Achievement of DAS28 score of < 2.6 at week 24

Study description

Background summary

Rheumatoid arthritis is a chronic inflammatory disease that affects the synovial joints of approximately 1% of the world's population (women three times more often than men). Although treatment options and efficacy have increased substantially in the past two decades, the disease cannot be cured or prevented. Therefore, rheumatoid arthritis still has a considerable effect on the quality of life of patients, not only because life-long medication is often required, but also because residual disease activity leads to progressive loss of function in the musculoskeletal system and extra-articular morbidity. 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, Aletaha & McInnes, 2016). Therefore, key future goals in the management of rheumatoid arthritis are the ability to induce long-lasting drug-free remission in patients with the disease. In addition, there are also patients who discontinue medication because of side effects, or because they do not want to take chronic medication. Neuromodulation has been suggested as a potential treatment option for patients.
Extensive evidence from small and large animal models, studies in porcine and human tissue and immune cells, and a pilot intraoperative clinical study have provided extensive evidence of immunomodulatory effect from Splenic Nerve Stimulation (SpNS) and suggests it differs from biological or targeted synthetic disease-modifying antirheumatic drugs.
Galvani bioelectronics developed a system to deliver electrical stimulation to the splenic neurovascular bundle in patients with moderate to severe RA or other inflammatory diseases. The implantable system is designed specifically for laparoscopic delivery to the splenic neurovascular bundle using surgical tools and accessories. The lead is attached to an Implantable Pulse Generator (IPG). 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. All components of this system are considered investigational.

Study objective

The Galvani Splenic Neuromodulation System consists of a lead, rechargeable implantable pulse generator, external components and accessories. The system is designed to deliver electrical stimulation to the splenic NVB in patients with moderate to severe RA or other inflammatory diseases. This study will evaluate the safety, tolerability, and effects of stimulating the splenic neurovascular bundle (NVB) with an active implantable medical device system in participants with moderate to severe RA.

Study design

Study GAL1040 (www.clinicaltrials.gov, NCT05003310) is a randomized control trial evaluating the safety, tolerability, and effects of stimulating the splenic NVB on the clinical signs and symptoms of RA. The study is being conducted in a maximum of 12 centres in the US and the Netherlands with an external Data safety Monitoring Board overseeing safety of GAL1040. A staggered enrolment will be applied with an implant suspension for safety analysis following 4 and again after approximately 10 participants implanted. Safety data will be submitted to the FDA to request continuation of study at both timepoints.

The study will consist of 4 study periods, including a Randomized Control Trial period (Period 1), an Open Label period (Period 2), a Treat-to-target period (Period 3), and a Long-term Follow-up period (Period 4) (see Figure 6 and 7 for the study overview). Participants with active rheumatoid arthritis (RA) will receive an implantable system and following a recovery period of at least 28 days after implant of the system, will be randomly assigned at Day 1 (of Period 1) to receive either active stimulation or sham-stimulation via this system for 12 weeks (84 days). The first 4 participants will receive Open-label stimulatie. Day 1 assessments will be used as a baseline. After the 12 weeks of randomized stimulation, all participants will enter an open label phase (Period 2) during which participants who achieved a clinical response (DAS28 improvement of greater than 1.2 points at week 12 relative to baseline) from active stimulation will continue active stimulation whereas participants who received sham stimulation as well as those who did not respond to active stimulation will be switched to baricitinib for 12 weeks.

At the 24 weeks* assessment, stimulation arm participants will have received either 24 weeks of active stimulation or 12 weeks of active stimulation followed by 12 weeks of baricitinib, whereas sham arm participants will have received 12 weeks of sham stimulation followed by 12 weeks of baricitinib. At the end of Period 2, participants who have achieved an initial clinical response (DAS28 improvement > 1.2 points) to therapy but have failed to achieve the treatment target (of DAS28 < 2.6) will enter the Treat-to-target period (Period 3); others will proceed to Period 4 (a 5-year Long-term Follow-up). During the Treat-to-Target period, participants will be treated with dual therapy (stimulation in combination with baricitinib) for up to 24 weeks, thereafter they will move to Period 4.The total duration for each participant in the treatment periods (Periods 1-3) - excluding screening and implant recovery and prior to entering Period 4 (LTFU) - is up to 48 weeks, depending on response to therapy). Period 4 (LTFU) provides long term safety follow up for all study participants for a period of 5 years. It also provides an escape to rescue treatment (if needed) and standard of care therapy for participants from previous periods experiencing uncontrolled systemic flares, lack of efficacy or intolerance to investigational therapy. Participants who did not receive Stim ON in the previous periods may receive Stim ON during Period 4, subject to a favourable benefit-risk assessment in the judgement of the treating rheumatologist.

Intervention

Participants with active rheumatoid arthritis (RA) will receive an implantable system by a laparoscopic surgical procedure and following a recovery period of at least 28 days after implant of the system, will be randomly assigned at Day 1 (of Period 1) to receive either active stimulation or sham-stimulation via this system for 12 weeks (84 days). After period 1, different treatment options are available depending on the disease activity of the patient including stimulation or the approved RA drug baricitinib.

Study burden and risks

During this clinical trial, the patient must undergo a laparoscopic surgery to place the implant. The patient is admitted to the hospital for 1 night to follow the patient for safety reasons. The implant operation is performed in the Catherina Hospital by an experienced and trained surgeon. In addition, the patient will have to come to the hospital several times to undergo various examinations to investigate the effect of the stimulation and the safety of the implant and stimulation, these are described in the patient information sheet. the examinations will consist of blood sampling, ECG, physical examination and questionnaires. The questionnaires are lists that are more often used for patients in RA clinical trials (SF-36 and HAD-Q) that evaluates, among other things, the mental and physical condition of the patients. If a patient feels uncomfortable with a question, it may be skipped. Furthermore, there are questionnaires specifically developed by Galvani, these are about the use and the patient's experience with the system.

During the screening, the patient undergoes a CT scan with a dye and an abdominal X-ray after implantation. There are risks associated with these imaging, including a small increased risk of cancer and risks associated with the contrast agent, The doctor will look at the medical data to see if the contrast agent is a risk for the patient. If risks are identified, the doctor may recommend specific treatments that can help reduce the risk of receiving the contrast agent. The participant may also feel discomfort when taking blood or taking an ECG. The risks associated with these procedures are no greater during the study than during routine clinical care and all examination procedures will be carried out by fully trained and experienced staff.

The operation and use of the investigational device may cause side effects/adverse effects. Because no patients have yet been implanted, the risks are difficult to predict until the research apparatus is implanted and used in more people. Although the implant procedure of the Galvani system is new, the procedures are based on existing operations

Risks of surgery

The risks that follow are seen as possible risks based on other operations on which the implant procedure is based:
• Bleeding from the spleen artery or other blood vessels may occur during surgery. In the rare case that the bleeding cannot be stopped, the spleen artery must be removed, or more invasive surgery is needed. The occurrence of spleen artery damage during longer, more complicated surgeries, such as operations targeting the esophagus, is low and occurs in less than 1% of surgeries. If the spleen artery is removed, the spleen is still supplied with sufficient blood through other veins.
• It is also possible that the splenic nerve is damaged during the operation, or during the placement or removal of the wire. Long-term effects of splenic nerve damage are not known, but surgeries that take place in this area do not report problems thought to be due to damage to these nerves.
• Nerve damage can cause the stimulation not to work as expected.
• There is a very small chance that the artery wall will be damaged during surgery, which can lead to a blood clot on the inside or around the blood vessel (pseudoaneurysm) and result in occlusion (blockage) or stenosis (narrowing). In all of these cases, the blood clot may move to the spleen or slow or stop blood flow to the spleen. If blood flow through the artery is reduced or stopped completely, it can change the way the spleen functions, but there are other arteries that supply the spleen with blood, so it's likely that the spleen won't need to be removed and can continue to perform its function.
* There is a small chance that other organs in the abdomen will be damaged or bleeded by the operation. In these cases, additional medication or surgery may be needed to repair the damage.
• It is recommended not to remove the implant, should it be decided to do so, the explant risks are similar to the implant risks.

Risks during the use of the research apparatus

• It is possible that the patient can feel the stimulation. The settings of the investigational device can be adjusted so that the patient is less bothered by it.
• It is possible that the stimulation can have unexpected effects on your body, such as change in blood pressure or heart rhythm.
• It is possible that a nearby organ (such as the pancreas) is affected by the stimulation that causes changes in its function. Frequent blood tests will check this.
• There is a small chance (<2%) that after the operation the area around the wire will become infected, this can usually be treated with medication. If these problems become severe, another operation may be needed to remove the wire if necessary.
• The risk of infection if your IPG needs to be placed on the outside of the muscle (in front of your abdomen) instead of in your abdominal wall is <5% This is due to the extra cut. It is also possible that you feel the IPG under the skin if it needs to be placed on the outside. Because the IPG is located outside the muscle, there is a risk of erosion (breakdown of the skin).

Erosion is expected to occur rarely and the surgical procedure is designed to reduce this risk, but if erosion occurs, it is possible that the IPG will need to be removed.
• The wire of the investigational apparatus and the stimulation can cause damage to tissues and organs, including the spleen nerve and the spleen artery, and it can take time for the damage to be noticed. If the spleen artery is damaged, the effect of the stimulation may be mixed. If the artery itself is damaged, it can lead to gradual weakening of the artery but rarely will it lead to bleeding.
• Damage to the artery by the wire can cause blood clots that can move towards the spleen. If blood flow through the artery is reduced or stopped completely, it can change the way the spleen functions, but there are other arteries that supply the spleen with blood, so it is very likely that the spleen does not need to be removed and can continue to perform its function.
• It is also possible for the wire or stimulator to move or break, which may cause the investigational device to stimulate the nerve or cause the investigational device to stimulate other areas of your body, which can lead to pain, discomfort, change in blood pressure or changes in heart rate. This may also prevent the investigational device from stimulating the nerve and the stimulation not working as expected.
Movement of the IPG or wire can also cause bleeding or damage to nearby tissues. If this happens, surgical intervention is needed to repair the implanted examination device.
• If a woman does becomes pregnant, the stimulation is set to OFF because the effect of stimulation on pregnancy is not known. It is also not known what the effect of the implant during pregnancy is on other organs.

All risks related to the surgical procedure and the implant have been evaluated according to Galvani's "risk-management process". Extensive risk analyses were carried out and mitigations were introduced. A detailed description of clinically relevant risks and their mitigations can be found in Table 2 of the protocol. In addition, a complete Verification and Validation (V&V) system was carried out in line with Galvani's ISO13485 certified quality management system, the results of that analysis are summarized in the Investigator brochure and IMDD. In the system V&V activities, a set of 1332 requirements were successfully evaluated. It was concluded that the Galvani System has an acceptable benefit/risk profile for the intended use and selected patient population in the closely monitored clinical trial. With implementation of the additional mitig

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Adult-onset RA of at least six months duration as defined by the 2010 ACR/EULAR classification criteria.
2. Male or female participants, 22-75 years of age inclusive at time of signing the informed consent.
3. Participants must have active disease as defined by at least 4 active swollen and at least 4 active tender joints (based on 28 joint count) and CRP >= 5.0 mg/L or DAS28-CRP>5.1. .
4. The participant must have had an Inadequate Response to at least 2 biologic DMARDs and/or JAK-inhibitors (JAKis) including at least one TNF inhibitor.
6. Participants must be receiving treatment with standard dose(s) of conventional synthetic DMARD(s) or the participant must have a documented history with a csDMARD and failed treatment due to ineffectiveness or intolerance.
7. Demonstrate, or simulate, ability to use the Galvani System components by
8. 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 OR Is a woman of childbearing potential (WOCBP)

and using an acceptable contraceptive method.

Exclusion criteria

1. Prior use of baricitinib or for whom baricitinib use is not recommended
2. Inability to provide informed consent.
3. Significant psychiatric disease or substance abuse.
4. History of unilateral or bilateral vagotomy.
5. Active or latent tuberculosis.
6. Known infection with human immunodeficiency virus (HIV); current acute or chronic hepatitis B or hepatitis C; previous hepatitis B.
7. Positive SARS COV 2 PCR screening test for COVID-19 infection (at the point of screening for this study).
8. Currently implanted electrically active medical devices (e.g., cardiac pacemakers, automatic implantable cardioverter-defibrillators).
9. Any prior investigational treatment (including small molecule drugs and/or biologic therapies) must be discontinued for at least 4 weeks or 5 half-lives, whichever is longer, prior to Day 1.
10. Patients with comorbid fibromyalgia.
11. Previous splenectomy.
12. Drug or alcohol abuse or dependence including opioid dependence or chronic opioid use.
13. Laboratory exclusion criteria: cytopenia as characterized by - anemia (hemoglobin < 8 g/dL), lymphopenia (ALC < 500 cells/mm3) and/or neutropenia (ANC < 1000 cells/mm3).
14. Any finding - which in the opinion of the investigator would interfere with the study interventions (including device implantation), study procedures and/or assessments, or create an undue risk for the participant.
15. Exclusion criteria related to the surgery and implant procedure (Surgeon Responsibility):
a. Patients with an epigastric abdominal wall thickness, epidermis to posterior rectus sheath at the level of the linea alba, greater than 2 cm based on screening ultrasound assessment and confirmed by CT-angiogram.
b. Patients with splenic artery luminal diameter greater than 7.4 mm or less than 3.0 mm dimension on CT-angiogram.
c. Type IV hiatal hernia and any hiatal hernia that produces a significant distortion of the local anatomy, especially the pancreas and/or splenic artery.
d. Gastric resection/mobilisation surgery with surgical access of the lesser sac.
e. Celiac axis, aneurysms or anatomy associated with congenital anomalies of the origin of the splenic artery.
f. 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.
g. Participants who do not have a demonstrable clear plane between the pancreas

and the splenic artery, at the interface site, in the preoperative CT angiogram.
h. Findings of cirrhosis or portal hypertension.
i. Documented history of pancreatitis with significant peripancreatic inflammation (CT evidence of necrosis, pseudocyst formation or significant retroperitoneal calcification).
j. Pancreatic abnormalities/mass/cyst/pseudocyst/lesions.
k. Any condition per the investigator's clinical judgment that qualifies the participant not fit for surgery.
l. BMI >= 33.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-02-2023
Enrollment:	12
Type:	Actual

Medical products/devices used

Generic name:	Galvani System
Registration:	No

Ethics review

Approved WMO

Date:	27-05-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2022
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	23-01-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-06-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-10-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-11-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT05003310
CCMO	NL78487.000.21