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

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Study GAL1039 (www.clinicaltrials.gov, NCT NL78487.000.21) is an Open Label study evaluating the safety, tolerability and effects of splenic nerve stimulation with Galvani's neuromodulation system. Since it is an Open Label study, the...

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

Summary

ID

NL-OMON55923

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 Period 1 en 2 of this study

are:

Evaluating the safety and tolerability of the Galvani spleen neuromodulation

system and stimulation of the splenic nerve as assessed by:

a. Incidence, causality, and severity of adverse reactions (AEs), serious

adverse reactions (SAEs), adverse reactions to devices (ADEs) and serious side

effects of devices (SADEs).

b. Laboratory safety assessments (clinical chemistry and haematology).

c. Vital signs measurements (blood pressure, heart rate, respiratory rate and

body temperature).

d. 12-Lead ECG monitoring.

Secondary outcome

1. Effect of stimulation on the change in pharmacodynamic and response

biomarkers:

Changes from baseline (Day 1) in the levels of LPS-inducible cytokine/

chemokine release, in whole blood assay at different timepoints after start of

stimulation

2. To evaluate the usability of the external Galvani System devices and

accessories:

Summarize feedback collected on questionnaires on the use of the external

Galvani System devices

3.To evaluate the participants' perception of therapy and sensation:

Summarize feedback collected on questionnaires

4. Evaluate device performance:

Tabulation of device deficiencies

Study description

Background summary

Rheumatoid arthritis is a chronic infiammatory 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 celis, and a pilot intraoperative clinical study have provided extensive evidence of immunomodulatory effect from Splenic Nerve Stimulation (SpNS) and suggests t 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

Study GAL1039 (www.clinicaltrials.gov, NCT NL78487.000.21) is an Open Label study evaluating the safety, tolerability and effects of splenic nerve stimulation with Galvani's neuromodulation system. Since it is an Open Label study, the effectiveness of the treatment will be evaluated as an exploratory objective. The study will also investigate the optimization of the frequency of stimulation.

Study design

Participants with active rheumatoid arthritis (RA) are laparoscopically implanted with the Galvani system and after recovering from surgery receive active stimulation for 12 weeks. The total study duration in Period 1 for each participant is approximately 5 months, with a screening period of 6 weeks, 4 weeks of recovery from surgery and a 'treatment period' of 12 weeks. The participants return to the clinic on pre-determined days for follow-up visits during the trial period. On day 42 and/or day 56, if study participants do not respond (sufficiently) to stimulation, stimulation parameters can be adjusted. At the end of Period 1 (day-84), participants will move on to Period 2 of the study. This is a long-term follow-up study up to 5 years after the participant started Period 2 to evaluate the safety of the Galvani system. In addition, the initial effectiveness will also be analyzed. In Period 2, changes in background medication are allowed and biological DMARDS or JAKi ("targeted" DMARDs) may be prescribed, either in combination with stimulation or without stimulation.
Additional stimulation paradigms may also be tested during this period (after submission and approval of an amendment to test alternative stimulation parameters).

Intervention

Participants with active rheumatoid arthritis (RA) receive an implantable system through laparoscopic surgery. The procedure is taking about 2 hours and the patients will stay 1 night in the hospital for safety follow-up. After a recovery period of at least 28 days after implantation of the system, they will start on day 1 (of Periode 1) to receive active stimulation through this system for 12 weeks (84 days). After Periode 1, different treatment options are available in Period 2 depending on the patient's disease activity, including stimulation whether or not in combination with Standard-of-Care (SoC) medication.

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 assessments will consist of blood sampling (approximately 25 times during the trial Period of 5 years), ECG, physical examination and questionnaires. A part of the questionnaires 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, the question can 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 and at the end of Period 1, the patient is undergoing 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 evaluate 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 not increased during the study compared when taken during routine clinical care and all assessments procedures will be carried out by fully trained and experienced staff.

The surgery and use of the investigational device may cause side effects/adverse effects. Because only a few patients have yet been implanted, the risks are difficult to predict until the investigational device is implanted and used in more people. Although the implant
procedure of the Galvani system is new, the procedures are based on existing

surgical procedures.
Risks of surgery:
The risks that follow are seen as possible risks based on other surgeries on which the implant procedure is based:
• Bleeding from the splenic artery or other blood vessels may occur during surgery. In the rare case that the bleeding cannot be stopped, the splenic artery must be removed, or more invasive surgery is needed. The occurrence of splenic artery damage during longer, more complicated surgeries, such as operations targeting the esophagus due to esophagus cancer, is low and occurs in less than 1% of surgeries. If the splenic 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 will not 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 are bleeding due to the surgery. 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 investigational device:
• 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 or not affected by it.
• It is possible that the stimulation can have unexpected effects on the 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 the 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 the patient feels 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 splenic nerve and the splenic artery, and it can take time for the damage to be noticed. If the splenic artery is damaged, the effect of the stimulation may be reduced. 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. It this happens, surgical intervention is needed to repair the implanted investigational device.
• If a woman does becomes pregnant, the stimulation is set to 0FF 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 1 of the protocol. In addition, a complete Verification and Validation (V&V) system was carried out in line with Galvani*s 1S013485 certified quality management system, the results of that analysis are summarized in the Investigator brochure and IMDD. It was concluded that the Galvani System has an acceptable benefit/risk profile for the intended use and selected patient popul

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Adult-onset RA of at least six months duration as defined by the 2010 ACR/EULAR classification criteria.
* Male or female participants, 22-75 years of age inclusive at time of signing the IC.
* Participants must have active disease as defined by:
* At least 3 swollen joints
* A DAS-CRP>3.2 and/or CRP >15 mg/L.
* The participant must have an IR to at least two biologic DMARD and/or a JAKi. Participants must have an appropriate washout as described below for previously used biological DMARDs or JAKI.
Biologic agents:
* Anakinra, etanercept; adalimumab; Infliximab; certolizumab pegol, golimumab, abatacept, tocilizumab, or other IL-6 blocking agents; tofacitinib, baricitinib or other JAKI*s must be discontinued 2 weeks before surgery.
* Rituximab, or other selective B lymphocyte depleting agents 6 month prior to Day 1.
* Any prior investigational treatment must be discontinued for 2 weeks or 2

half-lives, whichever is longer, prior to surgery.

Exclusion criteria

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

Exclusion criteria related to the surgery and implant procedure:
o Type IV hiatal hernia and any hiatal hernia that produces a significant distortion of the local anatomy, especially the pancreas and/or splenic artery.
o Gastric resection/mobilisation surgery with surgical access of the lesser sac.
o Celiac axis, aneurysms or anatomy associated with congenital anomalies of the origin of the splenic artery.
o 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.
o Participants who do not have a demonstrable clear plane between the pancreas and the splenic artery, at the interface site, in the preoperative computed tomography (CT) angiogram.
o Findings of cirrhosis or portal hypertension.
o Documented history of pancreatitis with significant peripancreatic inflammation (CT evidence of necrosis, pseudocyst formation or significant retroperitoneal calcification).
o Pancreatic abnormalities/mass/cyst/pseudocyst/lesions.
o Any condition per the investigator's clinical judgment that qualifies the participant not fit for surgery.
o Body Mass Index (BMI) >= 33.

o Splenic artery diameter as accessed by CT angiography <3.0 mm or >7.4 mm.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	18-01-2023
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Generic name:	Galvani System
Registration:	No

Ethics review

Approved WMO Date:	17-11-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-10-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	12-11-2024
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	NCT04955899
CCMO	NL84443.000.23