Randomized, double-blind, sham-controlled trial to investigate combined occipital and supra-orbital neuromodulation in resistant migraine. The RECLAIM study.

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To evaluate the safety and performance, including clinical benefit, of the PRIMUS System for the treatment of Resistant Migraine.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Headaches
Study type	Interventional

Summary

ID

NL-OMON57186

Source
ToetsingOnline

Brief title
The RECLAIM study.

Condition

- Headaches

Synonym
Migraine - headaches

Research involving
Human

Sponsors and support

Primary sponsor: Salvia BioElectronics B.V.
Source(s) of monetary or material Support: Salvia BioElectronics B.V.

Intervention

Keyword: Neurostimulation, Occipital Nerve Stimulation, Resistant Migraine, Supra-orbital Nerve Stimulation

Outcome measures

Primary outcome

Primary Safety Endpoint: The incidence of serious procedure, device and/or stimulation-related adverse events in all subjects at 12 weeks post-device activation.

Primary Effectiveness Endpoint: Difference between randomization arms, in proportion of subjects with >= 30% reduction in the number of Monthly Migraine Days (MMD) from the 4-week baseline period to weeks 9 through 12 of the randomized treatment phase.

Secondary outcome

Secondary Safety Endpoint: The incidence of serious procedure, device and/or stimulation-related adverse events in all subjects at the end of the study.

Secondary Effectiveness Endpoint:

- Difference between randomization arms in Cumulative Proportion of Responder Analysis (CPRA) based on percentage change in MMD, from the 4-week baseline period to weeks 9 through 12 of the randomized treatment phase.

- Difference between randomization arms in the mean change in number of Monthly

Migraine Days (MMD)2 from the 4-week baseline period to weeks 9 through 12 of the randomized treatment phase.

Exploratory Effectiveness Endpoints:

-Difference between randomization arms (SHAM vs Active) in mean change (from baseline) for the randomized treatment phase, at all applicable timepoints:

o Number of Monthly Migraine Days (MMD)

o Number of Monthly Crystal Clear Days (MCCD)

o Number of Monthly Headache Days (MHD)

o Number of Monthly Headache Free Days

o Onset of effect (based on >= 30% reduction in the number of Monthly Migraine Days (MMD)

o Number of Monthly Prevented Migraine Days (not compared to baseline)

o Proportion of patients with >= 30%, >= 50% and >= 75% reduction in the number of MMD

o Quality of Life (EQ-5D and Migraine Specific Quality of Life (MSQ))

o Migraine Functional Impact Questionnaire (MFIQ)

o Hospital Anxiety and Depression Scale (HADS)

o Work Productivity and Activity Impairment (WPAI:M)

o Headache duration, and pain severity (VAS 0-10),

o Headache load (* (duration X severity) of each day for a 28 days period)

o Monthly days with acute migraine-specific medication intake

o Change in the patient-identified Most Bothersome Symptom (MBS)

o Subject Satisfaction (Satisfaction Questionnaire)

o Patient Global Impression of Change (PGIC)

o Clinician Global Impression of Change (CGIC)

- Evaluation of the implantation procedure (Implanter Questionnaire)

- Evaluation of the use of the PRIMUS System (User Experience Questionnaire)

- Patient - MySalvia Device interaction (daily use, stimulation duration,

therapy compliance) (Device Statistics)

- Headache diary interaction and compliance

- Evaluation of the healing of the visible surgical area (forehead)

(de-identified photographs)

- Health care utilization

- Optional: analysis of physiological data, including pulse rate, physical

activity and sleep parameters collected by wearable health tracker

Study description

Background summary

The Salvia PRIMUS Peripheral Nerve Stimulation (PNS) System (System) is designed to provide subcutaneous neurostimulation to the branches of the trigeminal and occipital nerves. It is intended to modulate headaches* neural networks by utilizing mild electrical pulses. There are 2 stimulation waveforms: COMFORT (paresthesia-free stimulation) and STANDARD (paresthesia-provoking stimulation). The PRIMUS System comprises a long (supra-orbital) and a short (occipital) subcutaneous implant, a MySalvia device, a programmer, and surgical tooling.
The PRIMUS System consists of two integrated neurostimulator implants (a 17 cm and a 25 cm one), each with a lead, connected to a battery-free implantable pulse generator, a MySalvia device and a programming app that is installed on an off-the-shelf tablet. The 17 cm implant is implanted subcutaneously on the back of the head, at the level of the external occipital protuberance (EOP), to cover the branches of the left and right greater occipital nerves (ONS or Occipital Nerve Stimulation). The 25 cm implant is implanted on the forehead and covers the left and right supra-orbital nerves as well as the

supra-trochlear nerves (SONS or Supra-Orbital Nerve Stimulation). The MySalvia device is an external (non-implantable) unit providing the patient interface, and contains a rechargeable battery that can be recharged via a USB-C connector. The patient initiates the therapy by placing the MySalvia transmitters on the head, magnetically attaching them to the implants, and by pushing the ON/OFF button on the MySalvia Device. The stimulation settings can be set by using the Salvia Programmer.
The use of the PRIMUS System is investigational.

Study objective

To evaluate the safety and performance, including clinical benefit, of the PRIMUS System for the treatment of Resistant Migraine.

Study design

Multicenter, randomized, double-blind, sham-controlled, parallel-group, pre-market study with an adaptive trial design and an open-label extension phase.
62 patients will be enrolled, implanted with both the SONS and ONS implant and will be randomized 1:1 into 2 arms:
-
Arm 1: Treatment Group - Active stimulation: subthreshold
-
Arm 2: Control Group - SHAM stimulation: 0mA
The primary objective is to evaluate the proportion of subjects with >= 30% reduction in the number of Monthly Migraine Days (MMD) of the Treatment Arm versus the Control Arm. This will inform the power calculation of the pivotal trial.

Intervention

All subjects will have the PRIMUS System implanted in the occipital and supra-orbital region: ONS and SONS. The procedure can be performed under general anesthesia or local anesthesia with deep sedation.

Study burden and risks

The study will last approximately 30 months and includes 17 study visits. During these study visits, patients will also be regularly asked to complete questionnaires (including HADS, MSQ, EQ-5D-5L, WPAI-M, MBS, PGIC, Patient Satisfaction, User Experience, Blinding Index). Additionally, the patient will be asked to keep a daily headache diary. This is an electronic diary, and involves only one question if the patient has not experienced migraine/headache. Given that the study population consists of patients with chronic migraine or high-frequency episodic migraine, they may possibly benefit

from the regular hospital visits during which their headache diary is checked and possible changes in medication and/or health status can be discussed.

The PRIMUS implants are implanted under the skin using a minimally invasive technique during a short operation. Possible risks and side effects are minimal but can include: postoperative pain, sensitivity at the postoperative wound site, scarring, inadequate wound healing, infection, hematoma, blood vessel rupture, nerve damage, allodynia.

Treatment with the medical device may or may not prove beneficial for treating the migraine or alleviating the symptoms. The PRIMUS system delivers mild electrical pulses to the nerves under the skin (at the front and back of the head). Regular, daily stimulation may reduce nerve sensitivity, as well as the number of migraine days and/or the severity of migraine attacks. The following side effects can occur during stimulation: unpleasant paresthesia, pain, muscle contraction, fatigue.

Furthermore, there are some risks associated with the use of the medical device: allergic reaction, burn, redness, increased headache, pressure-related discomfort, discomfort from warming, sterile abscess, skin sensitivity, skin erosion, defect or malfunction requiring explantation.

The following procedures will be performed for the study:

The patient must remain stable on preventive medication and cannot start new medication for 3 months before the screening visit (and up to 6 months in the study).
Pregnancy test (if applicable)
Brain MRI (if no recent MRI < 4 year available)

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. Able and willing to provide written informed consent
2. Age >= 18 years and <= 84 years at the time of consent
3. Diagnosis of migraine as defined by the ICHD-3 Classification1 (with or without aura) with a history of chronic or high frequency episodic migraine for at least 1 year prior to screening:
- High Frequency Episodic Migraine (HFEM) defined as having on average >= 8 migraine days/month and < 15 headache days/month
- Chronic Migraine (CM) defined as having on average >= 8 migraine days/month and >= 15 headache days/month
4. Documented failure of preventive pharmacological therapies (failure meaning insufficient effect*, provoked unacceptable side-effects or contra-indicated)
In case of HFEM: failure of 3 or more other preventive therapies
In case of CM: failure of 3 or more other preventive therapies, from which at least one of the following two: CGRP mAbs or Onabotulinumtoxin A
5. Have at least 4 headache free days per month
6. Developed migraine before the age of 50
7. Stable on preventive migraine medication(s) and alternative treatment for at least three months prior to enrolment.
8. Agree not to change acute and/or preventive medication(s), nor to start any new medication or other therapies, during the baseline period and up to the 6 months study follow-up visit.
9. MRI available (not older than 4 years prior to study enrollment) or willing to undergo an MRI to exclude structural lesions potentially causing headache
10. Able and willing to complete a daily headache eDiary during the full duration of the study
11. Able and willing to comply with the requirements of the study visit schedule and self-assessment questionnaires

Exclusion criteria

1. Any other chronic primary or secondary headache disorder, unless the patient is able to clearly differentiate them from migraine attacks, based on the quality of the pain and/or associated symptoms.
2. Concomitant invasive and non-invasive neuromodulation
3. Previous exposure to any implantable neuromodulation device for headache
4. Have an existing Active Implantable Medical Device nearby the implant location (e.g. DBS, cochlear implant, *)
5. Metal implants in the skull (e.g. skull plates, seeds) nearby the implant.
6. Have a pacemaker or implantable cardioverter defibrillator (ICD)
7. Known history of Medication Overuse Headache in the last 6 months prior to enrollment
o Ergotamines or triptans on >= 10 days/month or,
o Opioids, including partial agonists, on >= 4 days/month or,
o NSAIDs or paracetamol on >= 15 days/month or,
o Combination analgesic >= 10 days/month
8. Use of onabotulinum toxin A injections for the treatment of migraine in the past 3 months.
9. Use of steroid infiltrations or IV-administration in the past 3 months.
10. Women of childbearing age who are pregnant, nursing, or not using contraception
11. Known to require an MRI scan during the study.
12. Psychiatric disorder or psychological condition that would, in the opinion of the investigator, interfere with the outcome of the study (e.g. severe depression, anxiety, rumination).
13. Confounding pain conditions other than migraine headache (e.g. fibromyalgia, chronic low back pain, complex regional pain syndrome), which could interfere with study procedures or pain reporting, as determined by the investigator.
14. Have a history of impaired wound healing or having factors that might impact normal wound healing.
15. Concomitant participation or planning to participate in another clinical study.
16. Have a pending or approved worker*s compensation claim, and/or ongoing planned litigation related to work.

Study design

Design

Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-01-2025
Enrollment:	20
Type:	Actual

Medical products/devices used

Generic name:	Primus system
Registration:	No

Ethics review

Approved WMO

Date:	18-12-2024
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NCT06450444
CCMO	NL86861.000.24