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Pilot study of safety and efficacy of unilateral MRI-guided focused ultrasound thalamotomy in tremor-dominant Parkinson's disease

Submission date
19/04/2023

Recruitment status
Recruiting

Registration date
10/05/2023

Overall study status
Ongoing

Last Edited
05/10/2026

Condition category
Nervous System Diseases

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims

Parkinson's disease is a progressive neurodegenerative disease characterised by gradually worsening tremor, muscle rigidity and difficulties with starting and stopping movements. The tremor in Parkinson's disease occurs at rest and becomes less prominent with voluntary movement. It typically occurs first in the distal upper extremities then moves proximally and spreads to affect other parts of the body over time. Treatment for Parkinson's disease includes supportive therapies and medications such as levodopa, dopamine agonists and monoamine oxidase B inhibitors. Surgery may be considered in people whose condition has not responded adequately to the best medical therapy. Surgical treatments include deep brain stimulation (DBS) and radiofrequency thalamotomy. Transcranial Magnetic Resonance guided focused ultrasound (MRgFUS) is a technology which allows permanent modification of brain function and relief of symptoms including tremors. MRgFUS thalamotomy, where focused ultrasound is targeted at the Ventral intermediate nucleus (Vim) of the thalamus, has been adopted worldwide as a minimally invasive alternative to established techniques such as Deep Brain Stimulation (DBS) in patients with medication-resistant Essential Tremor (ET). Clinicians based at Ninewells Hospital performed the first MRgFUS thalamotomy in Scotland in June 2021 and are the second unit in the UK able to deliver this therapy. The therapeutic effect of MRgFUS relies upon the permanent lesioning of the Vim by thermal coagulation necrosis caused by ultrasound-induced heating of the nucleus. Effective lesioning requires a 3-hour awake procedure during which patients receive repeated high-intensity focused ultrasound (HIFU) treatments. The intensity of each treatment is gradually increased to achieve thermal heating of the treatment target region to >50°C at which permanent lesioning and tremor suppression is achieved. HIFU involves the delivery of short (10-20 seconds) continuous ultrasound at intensities (~150-200W) necessary to produce the thermal effects. The potential benefits of unilateral MRI-guided focused ultrasound thalamotomy are that it: is less invasive than the other existing procedures; results in a faster recovery time; and allows for testing of the effects of sub-lethal doses before ablation. However, unlike deep brain stimulation, it can only be done on 1 side.

MRI guided focused ultrasound (MRgFUS) thalamotomy is not currently a NICE recommended treatment for Parkinson's Disease in the UK. The aim of this study is to demonstrate that this is a safe and efficient treatment.

Who can participate?
Males and females over the age of 30 years old with tremor-dominant Parkinson's Disease that is not responding to medication

What does the study involve?
Following a referral by their clinician, participants will receive a virtual research consultation then an in-person screening visit where eligibility will be confirmed, informed study consent taken and medical history recorded and a physical and neurological examination carried out. Demographic data will be collected along with results of the clinical and symptom rating scales, MRI and CT scans. If the participant's medical history indicates the possibility of metal being present in the skull, a safety X-ray will be performed. The participant then attends visit 3 where they consent to proceed with surgery and have some safety blood samples taken. The participant then receives the MRgGFUS thalamotomy and 24 hours later concomitant medication and adverse events will be checked and the participant completes another questionnaire and receives another MRI. If everything is satisfactory then the participant can leave. The participant returns 6 months later for a physical and neurological examination and another MRI. Participants will also complete the same questionnaires again. Any concomitant medications and adverse events will be recorded.

What are the possible benefits and risks of participating?
The aim of thalamotomy surgery is to reduce the tremor on one side of the body by around 50%. Typically the dominant side will be treated. MRgFUS thalamotomy can only be used to treat one side of your body. The tremor in the other, non-treated side will not be improved. The procedure is unlikely to improve head or voice tremor. Sensory disturbance (e.g. numbness or tingling of the limbs or face) affects 1 in 3 people (coloured figures in the illustration). In half of the people affected this resolves within weeks or months of the treatment but in half of the affected people, this can be permanent.
Balance disturbance (e.g. unsteadiness when walking) affects 1 in 3 people. In two-thirds of the people affected this resolves within weeks or months of treatment but it can be permanent in the other one-third of affected people.
Speech disturbance (e.g. slurring of speech) is generally a short-term complication that lasts weeks to months and affects around 1 in 20 people. A computed tomography head examination will be performed as part of routine clinical care. It may also be necessary to have an orbital eye x-ray as part of the pre-MRI screening process. This will not be the case for most patients and only in instances where there is reason to believe metal may be present in your skull. These procedures use ionising radiation to form images of the body and provide your doctor with clinical information. Ionising radiation may cause cancer many years or decades after exposure. Participants will not be exposed to any more ionising radiation as a result of taking part in this study.

Where is the study run from?
Ninewells Hospital & Medical School, University of Dundee (UK)

When is the study starting and how long is it expected to run for?
November 2021 to April 2030.

Who is funding the study?
Insightec Ltd (Israel)

Who is the main contact?
Dr Tom Gilbertson, t.gilbertson@dundee.ac.uk

Contact information

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Principal investigator

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Additional identifiers

Integrated Research Application System (IRAS)
311871

Protocol serial number

2-025-22

Study information

Scientific Title
Pilot study of safety and efficacy of unilateral MRI-guided focused ultrasound thalamotomy in tremor-dominant Parkinson’s disease

Acronym
SUNRISE

Study objectives
Transcranial Magnetic Resonance guided focused ultrasound (MRgFUS) thalamotomy is a safe, and tolerable treatment of tremors in patients with Parkinson’s disease.
Treatment of patients with Parkinson’s disease with MRgFUS thalamotomy will significantly improve their tremors immediately, and some improvement over baseline will be maintained during a 6-month follow-up period.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/04/2023, South East Scotland Research Ethics Committee 02 (2nd Floor, Waverley Gate, 2-4 Waterloo Place, Edinburgh, EH1 3EG, Scotland; +44 (0)131 536 9000; ruth.fraser4@nhslothian.scot.nhs.uk), ref: none provided

Primary study design
Interventional

Study design
Non-randomized interventional study

Study type(s)
Efficacy, Safety, Treatment

Health condition(s) or problem(s) studied
Parkinson's disease

Interventions
This is a pilot study designed initially to treat 10 patients with Parkinson's disease in Scotland who have medication-resistant tremor. Patients will be identified by their clinical teams in Health Boards across Scotland and referred to the MRgFUS thalamotomy clinic at Ninewells Hospital, Dundee. This is the same referral pathway that currently exists for patients with Essential Tremor (non-Parkinson's) and who are assessed in the MRgFUS Thalamotomy clinic as part of standard NHS care for Essential Tremor patients. The patients will receive study information and an invite letter from their current care of the elderly physician or neurologist. Patients who wish to take part can contact the research team directly with details provided or complete a response form on the letter to indicate their interest - this form will be included with the patient's referral.

On referral, the patients will receive an appointment for Nearme consultation to discuss the study and assess their suitability. Following the Nearme appointment, if the patient agrees to participate in the study they will be given an appointment to attend the MRgFUS thalamotomy clinic at Ninewells Hospital. At this appointment, informed consent will be taken and the patient will be screened against the inclusion and exclusion criteria. This will include neurological and neuropsychiatric assessments. Following these assessments, the patient will have MRI and CT scans to map the structure of their brain, pinpoint the target for treatment, and determine the density of their skull. The patient will receive the results of these tests, and whether they are suitable for MRgFUS thalamotomy at a telephone consultation approximately 6 weeks after the screening appointment. If they are not suitable they will be offered a further appointment with the clinical team to discuss the outcome.

Patients suitable for treatment will attend the MRgFUS clinic for an appointment with a consultant neurosurgeon toobtain their surgical consent for MRgFUS thalamotomy. Blood will also be taken for pre-surgical tests to assess liver and kidney function, red blood cell content and blood clotting. The patient will then attend the MRgFUS thalamotomy clinic for their thalamotomy treatment. The patient's head will be shaved and a metal headframe fixed to their skull under local anaesthetic. This frame will remain in place throughout the procedure. The thalamotomy will take around 1-3 hours. The patient is awake during the procedure, lying within an MRI scanner, and can have a friend/family member present with them, although the friend /family member will not be visible to the patient and the patient will be unable to move. During the procedure ultrasound treatments (lasting approximately 10 seconds) are delivered which produce short-lasting effects on tremor and allow assessment of potential side effects. The intensity of these ultrasound treatments is increased gradually to achieve permanent tremor relief. During the treatments it is common for patients to feel heating and discomfort around the headframe and also to feel dizzy and nauseous. Patients will be given pain relief, anti-sickness medication or mild sedation as needed by the clinical team. After the ultrasound treatment, a neurologist will assess the patient and additional pictures of the brain will be taken with the MRI scanner. After the treatment patients will stay overnight on a ward in Ninewells Hospital for observation. The following day they will receive a further MRI scan. Assuming the clinical team are satisfied with the response then patients will return to the MRgFUS clinic 6 months after treatment for assessment and further MRI scan.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Tremor measured using the Clinical Rating Scale for Tremor (CRST) during MRgFUS treatment

Key secondary outcome(s)
The following Secondary outcome measures are assessed on Day 1 and 6 months post-treatment:
1. Tremor measured using the Clinical Rating Scale for Tremor (CRST)
2. Symptoms associated with Parkinson’s disease measured using the Unified Parkinson's Disease Rating Scale (UPDRS)
3. Quality of life measured using the Parkinson's Disease Questionnaire (PDQ-39)
4. Adverse events will be recorded based on reported incidents in the participant’s medical notes at Visit 3 (24 hours after procedure) and Visit 4 (6 months after procedure)
5. Medication collection, and changes to medication, will be recorded in the patients medical notes at Visits 3 and 4.

Completion date

01/04/2030

Eligibility

Key inclusion criteria
1. Men and women age 30 years or older.
2. Subjects who are able and willing to give consent and are able to attend all study visits.
3. An established diagnosis of Parkinson’s Disease as confirmed from clinical history based upon UK Brain Bank criteria.
4. Tremor refractory to adequate trials of at least two medications, including levodopa equivalent dosage of 800 mg (total daily dose). An adequate medication trial is defined as a therapeutic dose of each medication or the development of side effects as the medication dose is titrated.
5. Tremor dominant PD defined by the UPDRS tremor scores (items 16,20,21) to the mean UPDRS postural instability/gait disorder scores (items 13-15,29,30) was ≥ 1.5
6. Vim nucleus of the thalamus can be targeted by the MRgFUS device. The thalamic region must be apparent on MRI such that targeting can be performed by measurement from a line connecting the anterior and posterior commissures of the brain.
7. Able to communicate sensations during the treatment.
8. Postural or resting tremor severity score of grade 3 or 4 in the most affected hand/arm as measured by the CRST (part A) rating scale while stable on medication (items 1-9).
9. Significant disability due to Parkinson’s tremor despite medical treatment (CRST score of 2 or above in any one of the items 16-23 from the Disability subsection of the CRST: [speaking, feeding other than liquids, bringing liquids to mouth, hygiene, dressing, writing, working, and social activities])

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
30 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Subjects with unstable cardiac status including:
1.1. Unstable angina pectoris on medication

1.2. Subjects with documented myocardial infarction within six months of protocol entry
1.3. Significant congestive heart failure
1.4. Subjects with unstable ventricular arrhythmias
1.5. Subjects with atrial arrhythmias that are not rate-controlled
2. Severe hypertension (diastolic BP > 100 on medication)
3. Significant speech impairment that would prevent communication during the procedure.
4. Unsteadiness when walking or turning and or instability on tandem walking during the formal examination.
5. Subjects with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, etc.
6. Known intolerance or allergies to the MRI contrast agent (e.g. Gadolinium).
7. Patient with severely impaired renal function with estimated glomerular filtration rate <30 mL /min/1.73m2 (or per local standards should that be more restrictive) and/or who is on dialysis.
8. History of abnormal bleeding and/or coagulopathy
9. Receiving anticoagulant (e.g. warfarin) or antiplatelet (e.g. aspirin) therapy within one week of focused ultrasound procedure or drugs known to increase risk or haemorrhage (e.g. Avastin) within one month of focused ultrasound procedure
10. History of immunocompromise including those who are HIV positive.
11. History of intracranial haemorrhage
12. Cerebrovascular disease (multiple CVA or CVA within 6 months)
13. Subjects with uncontrolled symptoms and signs of increased intracranial pressure (e.g., headache, nausea, vomiting, lethargy, papilledema).
14. Individuals who are not able or willing to tolerate the required prolonged stationary supine position during treatment (can be up to 4 hrs of total table time.)
15. Significant claustrophobia that cannot be managed with mild medication.
16. Subjects are unable to communicate with the investigator and staff.
17. Presence of any other neurodegenerative disease such as Parkinson-plus syndromes suspected on neurological examination. These include multisystem atrophy, progressive supranuclear palsy, dementia with Lewy bodies, and Alzheimer’s disease.
18. Presence of significant cognitive impairment as determined with a score ≤ 85 on the ACE-R.
19. Diagnosis of Dementia including Parkinson’s Disease Dementia (PDD).
20. Subjects with life-threatening systemic diseases that include and are not limited to the following will be excluded from the study participation: HIV, Liver Failure, blood dyscrasias, etc.
21. Subjects with a history of seizures within the past year.
22. Subjects with a history of psychosis will be excluded. Subjects with a history of self-harm /personality disorder, bipolar disorder, or moderately severe depressive illness will be excluded. For the purpose of this study, we consider moderately severe depressive illness to include any subject who:
22.1. has an IDS-SR score > 26
22.2. is currently under the care of a psychiatrist
23. Subjects with risk factors for intraoperative or postoperative bleeding: platelet count less than 100,000 per cubic millimetre, INR coagulation studies exceeding local institution laboratory standards, or a documented coagulopathy
24. Subjects with brain tumours
25. Any illness that in the investigator's opinion precludes participation in this study.
26. Pregnancy or lactation.
27. Legal incapacity or limited legal capacity.
28. Subjects who have had deep brain stimulation or a prior stereotactic ablation of the basal ganglia
29. Subjects who have been administered botulinum toxins into the arm, neck, or face for 5 months prior to Baseline.
30. Subjects who have an Overall Skull Density Ratio of 0.3 or less as calculated from the

screening CT.

Date of first enrolment
01/05/2023

Date of final enrolment
01/10/2029

Locations

Countries of recruitment
United Kingdom

Scotland

Study participating centre
Ninewells Hospital
Ninewells Avenue
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Sponsor information

Organisation
University of Dundee

ROR
https://ror.org/03h2bxq36

Funder(s)

Funder type
Industry

Funder Name
Insightec Ltd

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 3	17/04/2023	24/04/2023	No	Yes
Participant information sheet	version 5	15/01/2024	13/03/2024	No	Yes
Protocol file	version 1	10/11/2022	24/04/2023	No	No