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Sonodynamic therapy using focused ultrasound in glioblastomas

Submission date
20/11/2025

Recruitment status
Recruiting

Registration date
07/04/2026

Overall study status
Ongoing

Last Edited
07/05/2026

Condition category
Cancer

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

Plain English summary of protocol

Background and study aims
Despite progress made in many cancer treatments, high-grade gliomas (HGG) remain an extraordinary challenge. Their aggressive and infiltrative nature, the limited efficacy and inherent risk of surgical resection combined with radiotherapy, and the difficulty in delivering anticancer drugs to the brain, make the prognosis for patients with gliomas grim. Therefore, new and less-invasive alternatives to existing procedures are needed.
Sonodynamic therapy (SDT) represents an emerging approach that offers the possibility of noninvasively eradicating solid tumours. It involves the delivery of a non-toxic chemical agent that selectively accumulates into target areas and the subsequent exposure of the targeted tissue to relatively low-intensity ultrasound. These procedures (sensitization and ultrasound exposure) are both per se harmless, but, when combined, result in activation of the chemical agent and subsequent cytotoxic events limited to the target tissue volume. SDT offers significant advantages because ultrasound energy can be tightly focused and delivered through the intact skull to deep areas of the brain.
5-ALA is a PpIX precursor that selectively accumulates in HGGs because of an enhanced uptake and metabolism from tumour cells. It is used for intraoperative guidance in surgery as tumour tissue shows fluorescence under certain light conditions due to PpIX accumulation, as compared to the normal surrounding parenchyma. It is therefore a good candidate for SDT. 5-ALA can exert sonodynamic effects against HGGs, as it has been shown in several pre-clinical studies. Unpublished pre-clinical data on a safety experiment conducted at the University of Virginia showed that SDT with 5- ALA was not exerting a toxic effect to the normal brain.
The idea of the present study is to investigate the antitumor effects of SDT in patients affected by HGGs attained with low-frequency focused ultrasound in combination with the systemic administration of 5-ALA.

Who can participate?
Patients aged between 18 and 70 years with suspected primary lobar glioblastoma

What does the study involve?
Participants undergo SDT with magnetic resonance-guided focused ultrasound (MRgFUS) treatment a week before they are scheduled for surgery. Three hours before the scheduled SDT procedure, participants will receive a dose of 20 mg/kg administered orally of 5-ALA. The

participant's head will be shaved completely and a frame will be fixed to the skull for the duration of the procedure. A series of MR images will be acquired to identify the target area and plan the actual treatment. A series of sonications will be initiated and maintained for 20 minutes. The treatment may require many sonication series, therefore the total treatment time could be up to 2-3 hours. During the procedure repeated neurological exams will be performed and participants will be asked to report all sensations (i.e., disorientation/dizziness, pain, numbness, etc) occurring during the procedure so that adjustments can be made to the treatment plan. A final MRI with contrast will be done at the end of the procedure to assess the treatment area. Following the procedure, the head frame will be removed and participants will be taken off the treatment table and admitted to the hospital overnight. Participants will undergo an additional MRI scan 1 day after the procedure and if they are stable will be discharged from hospital. Participants will be asked to undergo follow-up neurological and physical examination and an MRI scan 1 week after the SDT with MRgFUS procedure but before surgery.

What are the possible benefits and risks of participating?
MRgFUS risks: claustrophobia, deep venous thrombosis, pain, hypertension/hypotension, bradycardia, neurological deficits, numbness or tingling of the face, fingers, imbalance, ataxia, dysmetria, tinnitus, dizziness, aphagia, dysphagia, dysgeusia, damage to the optic nerve, headframe pain, oedema, burning or bleeding, infection and bruising from IV line, events associated with comorbid conditions or unforeseen circumstances, drug reactions: nausea or vomiting, overdose or mis-dosing in error, misalignment, mistargeting or reflection of the Exablate beam, heating of structures in the FUS backbeam or forebeam, skin burns (>2o) with ulceration of the skin, scar formation, loss of sensation, atrophy, bone in the sonication pathway: bone necrosis, scalp in the sonication pathway: subdural bleeding, vein thrombosis, cortex heating, seizures, motor, sensory, auditory, visual, speech symptoms.
Risk of contrast agent: headache, nausea, localized injection site coldness, dizziness.
Risks of 5-ALA: anemia, thrombocytopenia, leukocytosis, increase in blood enzyme levels.
Risks of SDT with 5-ALA using MRgFUS: This is an early human pilot trial and early evidence shows no significant side effects in 5 patients. The platform for ultrasound administration has been used for blood brain barrier disruption (BBD) with over 100 temporary disruption procedures to date with minimal procedure related, mild, transient events. No serious or severe adverse device effects have been reported at this time. It is the purpose of this trial to gain experience that will allow us to further determine the safety of Exablate SDT. It is expected that a predominance of SDT specific events would be related to brain oedema and haemorrhage. These complications are unlikely, but if they occur, they may require medical management with increased dexamethasone and/or mannitol. Should pressure build up inside the skull, the bone flap from the craniotomy could be removed or the craniotomy expanded to relieve increased pressure.
These mechanisms may cause transient or permanent local neurological deficits or symptoms. Permanent neurological deficits or death could possibly result. However, no sonications will be performed in the area outside the Gadolinium enhancement, notably areas with augmented FLAIR signal on MR and safety pre-clinical studies showed no harmful effect on normal cerebral structures. There is a risk of imprecise targeting of the focal point, and haemorrhage or tissue damage outside of the planned treatment volume. If this occurs, it is possible that serious neurological deficit or even death could result. To limit the risk of this occurring, the treatment process includes a mandatory verification step that requires the operator to first check the alignment of the subject anatomy, the focal point of the transducer and the MR imaging system. This procedure, done while the subject is in position for treatment, uses a very low energy sonication to confirm of the alignment of the focal point and the targeted treatment point in all three axes. For each sonication delivered during treatment, the operator gets continuous feedback on the position of the intended treatment point superimposed on the thermal

dosimetry image and can make corrections where required if there is an elevation in tissue temperature. At any point in the treatment process this low-power verification of the localization may be repeated to ensure proper system focusing. There is a very low risk of cavitation in the tissue at the focal point: cavitation is the collapse of rapidly developed gas bubbles at the focal point due an extreme intensity of ultrasound excitation.
This rapid collapse could cause high pressure, shock waves and high temperatures. However, we believe that through proper system design and careful selection of the system operation envelope, there is very minimal risk of cavitation.
All patients will be screened for prior to treatment for identification of risks and mitigation planning where feasible and appropriate. Patients will be educated on what to expect during the procedure and the importance of maintaining their position. Head immobilization will be used to limit movement.
The treatment procedure is performed in the MR scanner, with images acquired during treatment. This monitoring can detect changes in temperature, potential tissue damage, bleeding, or if brain or blood vessels are injured by heat.
The medical team will be in close proximity throughout the sonication to monitor the patients' medical status. Both patient and neurosurgeon have a stop switch that can instantaneously interrupt the energy delivery at any time for any reason that may cause concern. Following evaluation, treatment can resume.

Where is the study run from?
Imperial College Healthcare NHS Trust (UK)

When is the study starting and how long is it expected to run for?
February 2026 to November 2027

Who is funding the study?
Focused Ultrasound Foundation (UK)

Who is the main contact?
Tina Stoycheva, tina.stoycheva@nhs.net

Plain English summary under review with external organisation

Contact information

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Additional identifiers

Integrated Research Application System (IRAS)
1012243

Central Portfolio Management System (CPMS)
72663

Study information

Scientific Title
A Phase I study to evaluate the safety and feasibility of sonodynamic therapy with 5-aminolevulinic acid using exablate MRI-guided focused ultrasound in the treatment of cerebral glioblastomas

Study objectives
Primary objective:
The main goal of the present study is to investigate the safety and feasibility of SDT in patients affected by glioblastomas attained with low-frequency focused ultrasound in combination with the oral administration of 5-ALA.

Secondary objective:
To evaluate treatment efficacy.

Ethics approval required
Ethics approval required

Ethics approval(s)
Submitted 17/11/2025, East of England - Cambridge Central Research Ethics Committee (-, -, -, United Kingdom; -; cambridgecentral.rec@hra.nhs.uk), ref: 25/EE/0263

Primary study design
Interventional

Study design

Prospective single-arm non-randomized study

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Gliobastoma

Interventions
Participants can undergo SDT with MRgFUS treatment a week before they are scheduled for surgery.

Three hours prior to the scheduled SDT procedure, participants will receive a dose of 20 mg/kg administered orally of 5-minolevulinic acid (Gliolan®). The participant's head will be shaved completely and a stereotactic frame will be fixed to the skull for the duration of the procedure. The participant will be positioned supine and headfirst on the MR/ExAblate 4000 Type 2 therapy table with the 220 KHz system. The hemispherical helmet containing the elements of the ExAblate transducer will be positioned over the convexity of the participant’s head in the treatment position according to measurements taken from the imaging session(s). A series of MR images will be acquired to identify the target area, and plan the actual treatment. A central point in the targeted volume will be sonicated at low power to confirm the targeting accuracy on the MR thermometry images. Focal point position and/or transducer location will be adjusted as necessary. A series of 5 W/cm2 burst sonications (10% duty cycle) will be initiated and maintained for 20 minutes. The treatment may require many sonication series, therefore the total treatment time could be up to 2-3 hours. During the procedure repeated neurological exams will be performed and participants will be asked to report all sensations (i.e., disorientation/dizziness, pain, numbness, etc.) occurring during the procedure so that adjustments can be made to the treatment plan.

A final MRI with contrast will be done at the end of the procedure to assess the treatment area. Following the procedure, the head frame will be removed and participants will be taken off the treatment table and admitted to the hospital overnight.
Participants will undergo an additional MRI scan one day after the procedure and if they are stable will be discharged from hospital.

Participants will be asked to undergo follow-up neurological and physical examination and an MRI scan one week after the SDT with MRgFUS procedure but prior to surgery.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Gliolan [5-Aminio laevulinic acid, 5 amino laevulinic acid]

Primary outcome(s)
Safety: Safety will be evaluated by patient examination and MRI images during the treatment, immediately post-treatment and on day 1 and week 1 post-treatment.
Feasibility: The extent of the sonicated area will be calculated at the end of the procedure in

order to evaluate the targeted area. Tumour regression will be determined by contrast enhancement on post-procedural serial contrast-enhanced MR images. Pathological examination and immunohistochemistry of the resected specimen will also be utilized to verify the amount of cell apoptosis and necrosis.

Key secondary outcome(s)
Efficacy: Tumour volume changes post-procedure according to MRI imaging immediately post-treatment and on day 1 and week 1 post-treatment

Completion date
01/11/2027

Eligibility

Key inclusion criteria
1. Men and women between 18 and 70 years
2. Suspected primary lobar glioblastoma clearly measurable on the basis of Response Assessment in Neuro-Oncology (RANO) criteria
3. Brain glioblastomas located in a surgically accessible brain region for resection
4. The targeted tumour resection volume measures between 1 and 5 cm in diameter
5. Karnofsky rating 70-100
6. ASA score 1-314
7. Able to attend all study visits
8. Able and willing to give informed consent

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
70 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Brain glioblastoma presenting with the following characteristics:
1.1. Brain oedema and/or mass effect that causes midline shift of more than 10 mm
1.2. Evidence of recent intracranial haemorrhage within the targeted tumour volume
1.3. Calcifications in the focused ultrasound sonication path (system tools may not tailor the treatment around these calcifications)
2. The sonication pathway to the tumour involves either:

2.1. More than 30% of the skull area traversed by scars, scalp disorders (e.g. eczema), or atrophy of the scalp
2.2. Clips, shunts, or other metallic implanted objects in the skull or the brain
3. Cardiac disease or unstable hemodynamic status including:
3.1. Documented myocardial infarction within six months of enrolment
3.2. Unstable angina on medication
3.3. Congestive heart failure
4. Severe hypertension
5. Anti-coagulant therapy or medications known to increase risk of haemorrhage within washout period prior to treatment.
6. History of a bleeding disorder, coagulopathy or with a history of spontaneous tumor haemorrhage
7. Abnormal level of platelets (<100000) or INR >1.3
8. Cerebral or systemic vasculopathy
9. Known allergy sensitivity or contraindications to gadolinium
10. Contraindications to MRI such as non-MRI-compatible implanted devices
11. Subjects not fitting comfortably into the MRI scanner
12. Difficulty lying supine and still for up to 4 hours in the MRI unit or claustrophobia
13. Positive pregnancy test (for pre-menopausal women)
14. Severely impaired renal function with estimated glomerular filtration rate <30 ml/min/1.73m2 and/or on dialysis
15. Respiratory: chronic pulmonary disorders, e.g. severe emphysema, COPD, pulmonary vasculitis, or other causes of reduced pulmonary vascular cross-sectional area
16. Any illness or medical condition that in the investigator's opinion precludes participation in this study
17. Patients unable to sign a consent form

Date of first enrolment
01/02/2026

Date of final enrolment
01/11/2026

Locations

Countries of recruitment
United Kingdom

Study participating centre
Imperial College Healthcare NHS Trust
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St Marys Hospital
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Sponsor information

Organisation
Imperial College Healthcare NHS Trust

ROR
https://ror.org/056ffv270

Funder(s)

Funder type

Funder Name
Focused Ultrasound Foundation

Alternative Name(s)
Foundation for Focused Ultrasound, FUS Foundation, FUF, FUSF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date