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Study of Sonazoid™ in patients under the age of 18

Submission date 28/09/2023	**Recruitment status** Recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 18/12/2023	**Overall study status** Ongoing	
Last Edited 23/01/2025	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Liver tumours, 40% of which are benign, account for 1% to 4% of all solid tumours in children. The benign tumours are mainly haemangiomas, liver hamartomas, and liver cell adenomas. The malignant tumours are mainly hepatoblastoma, hepatocellular carcinoma (HCC), malignant liver mesothelioma, and rhabdomyosarcoma. The differential diagnosis of liver masses in children is generally based on the child's age, the clinical evaluation (including alpha-fetoprotein test results), and imaging characteristics.
Liver tumours seldom produce clear symptoms and signs in the early stages, and they progress rapidly. As a result, most liver tumours are not diagnosed until the middle or late stages. To improve survival among patients with liver tumours, clinicians must find the liver tumours as early as possible and determine whether the tumours are benign or malignant. Conventional ultrasonography is commonly used for screening and is preferred as the first-line imaging technique for children. Not only does it have a wide range of applications and a high diagnostic yield, but it is well accepted by patients and their parents. It can be performed in the examination room with the parents present, allowing real-time imaging and direct interaction with the patient and parents.
CEUS (Contrast Enhanced Ultrasonography) is a non-invasive imaging technology that can continuously and dynamically observe blood perfusion in tumours in real-time through the injection of a contrast agent to enhance the blood flow reflux signal in the human body. Consequently, CEUS is useful for visualising capillaries and tissue perfusion in the human body. The purpose of this current study is to evaluate the use of Sonazoid™ perfluorobutane (PFB) microbubbles as a contrast medium for CEUS for the evaluation of solitary liver masses in children.

Who can participate?
Patients below the age of 18 years who have been diagnosed with one or more untreated abnormal masses in the liver, called a focal liver lesion (FLL)

What does the study involve?
If a patient has multiple abnormal masses, the study doctor must select one that will be referred to as "the target lesion" at his/her discretion. The diagnosis of benign or malignant for the target lesion of interest will be established by the study doctors using all available clinical

information, including the results of biopsy (tissue sample taken from the mass), if available, and the imaging procedures (contrast-enhanced CT or contrast-enhanced MRI).
After an initial unenhanced (pre-contrast) ultrasound (US) examination of the target lesion, a single dose of Sonazoid™, dosed according to body weight, will be injected into a vein of the patient and a Contrast Enhanced Ultrasound (CEUS) examination will be performed, and images for both these US examinations will be collected.
The unenhanced US and CEUS images will be assessed by three independent readers who are not allowed to know the patient identification or clinical diagnosis for the target lesion provided by the study doctors, following standard guidelines for ultrasound interpretation. The diagnoses made by the independent readers, based on the unenhanced US and the CEUS results, will be compared with the reference diagnosis for the target lesion made by the study doctors. This comparison will allow sensitivity and specificity information about the unenhanced US and CEUS images to be calculated.
Clinical safety data, including blood pressure, heart rate, breathing rate, oxygen levels in the blood, blood and urine analysis results, physical examination and injection site observations will be collected throughout the study. Safety will also be evaluated by monitoring the patients for the occurrence of adverse events.

What are the possible benefits and risks of participating?
Participation in this study will not benefit patients directly. Sonazoid™ is being tested to see if it can help with disease diagnosis. It is not a treatment or therapy that would make the patient feel better but participation may help to improve the understanding of how Sonazoid™ works in patients under the age of 18 which may benefit patients in the future. For some patients participating in this study, there might be a benefit relating to the characterisation of their liver masses and/or detection of new masses in their liver.
The gas component of Sonazoid™ is eliminated by exhalation. However, the presence of lung disease was not associated with an increase in AEs after the use of Sonazoid™. Nor were there any noteworthy trends in AEs among subjects with renal impairment. Unlike the ultrasound contrast agents that are produced at the point of use or that generate bubbles in vivo, the Sonazoid™ microbubbles are of known size distribution. Sonazoid™ is subject to manufacturing controls during its production and batches are subject to quality assurance assays. The Sonazoid™ microbubbles are of a relatively small and uniform size, with a mean diameter between 2.4 and 3.5 µm. In addition, Sonazoid™ is filtered through a 5 µm filter before injection. For these reasons, the risk of a stroke or transient ischaemic attack after Sonazoid™ administration is believed to be extremely low, even if a right-to-left shunt was present in the subject. Nevertheless, caution should be exercised in patients with known right-to-left shunts.
Another risk consideration involves patients with a hypersensitivity to eggs or egg products. Sonazoid™ contains a surfactant produced from eggs and thus may contain trace amounts of egg proteins. Rarely, hypersensitivity reactions to eggs or egg proteins (including symptoms of generalised urticaria, difficulty in breathing, swelling of the mouth and throat, hypotension, or shock) may occur. The risks of Sonazoid™ administration in subjects with known hypersensitivity to eggs have not been fully evaluated. However, because anaphylactic reactions have been observed with other intravenously injected drugs, the potential for hypersensitivity reactions after Sonazoid™ injection cannot be excluded. Because of the potential risk, care should be exercised with patients having a history of severe hypersensitivity (anaphylactic allergy) to eggs or egg products. Patients with known hypersensitivity to eggs or egg products are excluded from this study.
The risk of placing a catheter includes discomfort around the injection area with possible bruising and/or, bleeding. This can also cause infection, and rarely, fainting or nerve damage. The volume of blood collected will not exceed the international ethics and regulations guidance.

Where is the study run from?
GE HealthCare Ltd (UK)

When is the study starting and how long is it expected to run for?
September 2023 to October 2026

Who is funding the study?
GE HealthCare Ltd (UK)

Who is the main contact?
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Contact information

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Scientific

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Clinical Trials Information System (CTIS)
2023-505569-95

Integrated Research Application System (IRAS)
1007450

Protocol serial number
GE-045-401, IRAS 1007450

Study information

Scientific Title
A Phase IV, open-label, non-randomized, multicenter study to evaluate safety and efficacy of intravenous administration of Sonazoid™ for contrast-enhanced ultrasound liver imaging in paediatric patients

Study objectives
Primary objective:
To evaluate the diagnostic accuracy of ultrasound images enhanced with Sonazoid™ (perflubutane microbubbles) for differentiating benign vs malignant focal liver lesions in paediatric patients during vascular phase imaging.

Secondary objectives:
1. To assess the safety profile of intravenous administration of Sonazoid™ in the paediatric population.
2. To compare the diagnostic accuracy of Sonazoid™-enhanced ultrasound images vs unenhanced ultrasound images for differentiating benign from malignant focal liver lesions (FLL) in paediatric patients during imaging.
3. To compare the detection of focal liver lesions (FLL) in Sonazoid™-enhanced ultrasound images vs unenhanced ultrasound images in paediatric patients during imaging.
4. To assess whether the use of Sonazoid™-enhanced ultrasound images vs unenhanced ultrasound images affects the reader’s confidence in their diagnosis of benign vs malignant FLL in paediatric patients during vascular phase imaging and Kupffer phase imaging.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 16/12/2023, Hampstead Research Ethics Committee (2 Redman Place Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8227, +44 (0)207 104 8284, +44 (0)207 104 8345; hampstead.rec@hra.nhs.uk), ref: 23/LO/0878

Study design
Open-label non-randomized multicentre prospective study

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Focal liver lesions

Interventions
This Phase IV, open-label, non-randomised, multicentre prospective study in Europe will enrol paediatric patients who are presenting with ≥1 confirmed untreated target FLL. If a patient has multiple FLLs, the Investigator must select the target lesion at their discretion. Where possible, the target lesion should be a clearly visible and accessible lesion that could be easily followed during the non-contrast-enhanced (CE) ultrasound examination and all phases of the CE ultrasound (CEUS) examination. The reference diagnosis/standard of truth for the target lesion of interest will be established by the principal investigators/sub-investigators on the basis of all available clinical information, including the results of biopsy, if available, and the dynamic CE-computed tomography (CECT) or CE-magnetic resonance imaging (CEMRI) examination required for the study.

Following unenhanced (pre-contrast) ultrasound imaging of the target FLL, a single dose of Sonazoid™, dosed according to body weight (0.12 µL microbubbles/kg, 0.015 ml/kg), will be intravenously administered to each patient, and a CEUS examination will be performed, with images acquired as specified in the Imaging Manual.

The unenhanced ultrasound and CEUS images will be assessed by three independent blinded readers following the World Federation for Ultrasound in Medicine and Biology-European Federation of Societies for Ultrasound in Medicine and Biology (WFUMB-EFSUMB) guidelines for adults, in accordance with the Independent Review Charter. The diagnoses based on the unenhanced ultrasound and the CEUS results will be compared with the reference diagnosis /standard of truth for the target lesion. The diagnostic accuracy, sensitivity and specificity of the unenhanced ultrasound and CEUS images will then be calculated. Clinical safety data will be collected throughout the study. Safety will be evaluated by monitoring subjects for the occurrence of AEs.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Sonazoid™ [perflubutane]

Primary outcome(s)

The accuracy, sensitivity and specificity of the diagnosis based on the independent blinded read of the Sonazoid™-enhanced imaging for lesion differentiation (benign or malignant FLLs) during vascular phase imaging. The WFUMB-EFSUMB guidelines for interpreting CEUS of the liver in adults shall be used for interpreting the images and the subject's baseline diagnosis (well-established by CECT, CEMRI or biopsy) will be used as the reference diagnosis/standard of truth.

Key secondary outcome(s))

1. Accuracy, sensitivity and specificity of the diagnosis (benign or malignant FLL) based on the Sonazoid™-enhanced imaging by vascular phase imaging, as compared with the unenhanced ultrasound imaging, when the baseline diagnosis is used as the reference standard.
2. Accuracy, sensitivity and specificity of the diagnosis (benign or malignant FLL) based on the Sonazoid™-enhanced imaging by vascular phase and Kupffer phase imaging, as compared with the unenhanced ultrasound imaging, when the baseline diagnosis is used as the reference standard.
3. The difference in the diagnostic confidence score for the unenhanced ultrasound imaging and that for the Sonazoid™-enhanced ultrasound imaging based on the vascular phase.

Each of the outcome measures are based upon the independent blinded read of the Sonazoid™-enhanced imaging for lesion differentiation. The independent blinded reads are to be conducted in a summative manner at the end of the study. According to the current study timelines the blinded reads shall be approximately mid-December (accounting for a last subject scan date of approximately 26/11/2025).

Completion date

31/10/2026

Eligibility

Key inclusion criteria

1. The subject is <18 years of age on the day of consent
2. The subject has at least 1 untreated FLL with ≤8 lesions (excluding cysts), with ≤10 cm confirmed in a diagnostic examination performed in the past month (or past 3 months if the lesion was benign) and that could be visualised by unenhanced (not contrast-enhanced) US imaging.
3. The subject has had a dynamic CECT or CEMRI examination within the past month or was scheduled to have one in the month following inclusion in the study and the original images (or copies thereof) are/would be available.
4. The subject can comply with study procedures.
5. Parents or legally authorised representatives have signed the Informed Consent Form approved for this study by the Ethics Committee. The form will indicate that the patient (and/or a legally acceptable representative) has been informed of all pertinent aspects of the study. Patients who are able to provide assent have signed an age-appropriate paediatric assent form.
6. Post-menarcheal female patients must have a negative urine pregnancy test at screening and at pre-dose on the dosing day.
7. Post-menarcheal female patients and male patients who are sexually active with a partner of childbearing potential must be practicing abstinence or be using an effective form of birth control (See Section 8.6) for ≥30 days before being enrolled in the study.

Participant type(s)

Patient

Healthy volunteers allowed
No

Age group
Child

Upper age limit
18 years

Sex
All

Key exclusion criteria
1. The subject has a known or suspected hypersensitivity to any of the components of Sonazoid™, including a history of allergies to eggs or egg products (i.e., manifested by full body rash, respiratory difficulty, oral or laryngeal swelling, hypotension, or shock).
2. The subject has an acute clinically fatal condition (i.e., the expected survival is ≤6 months).
3. The subject has previously received Sonazoid™ or another ultrasound contrast agent within the past 30 days.
4. The subject has undergone or was undergoing systemic or loco-regional chemotherapy or radiation therapy.
5. The subject is participating in another clinical trial with an unregistered medicinal product, or less than 30 days has passed since the subject completed participation in such a trial.
6. The subject is a pregnant or lactating female or is a female of childbearing potential not using an acceptable form of birth control (negative urine pregnancy test also required).
7. The physician judges that a large-enough needle (24-gauge or larger) cannot be inserted.

Date of first enrolment
20/01/2025

Date of final enrolment
31/07/2026

Locations

Countries of recruitment
United Kingdom

England

Germany

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King’s College Hospital
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Study participating centre
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Sponsor information

Organisation
GE HealthCare Ltd

Funder(s)

Funder type
Industry

Funder Name
GE Healthcare

Results and Publications

Individual participant data (IPD) sharing plan

The data-sharing plans for the current study are unknown and will be made available at a later date

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 1.0	25/09/2023	09/10/2023	No	Yes
Participant information sheet	version 4.0	30/04/2024	22/01/2025	No	Yes