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A first-in-human safety study of the novel adrenal PET tracer [18F]CETO

Submission date
04/05/2020

Recruitment status
No longer recruiting

Registration date
19/05/2020

Overall study status
Completed

Last Edited
30/12/2022

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
At least one-quarter of the UK adult population has high blood pressure (hypertension), a major risk factor for heart attacks and stroke. Primary aldosteronism (PA), a treatable form of hypertension, accounts for 5-10% of all cases, and 20-25% of difficult to control hypertension. It is challenging to determine whether one adrenal gland is the source of PA (which is potentially curable with surgery) or both glands (which would require long-term drug treatment). Existing lateralising procedures (i.e. investigations to distinguish one from two gland involvement e.g. CT or MRI scan) have significant limitations. Accordingly, most patients must undergo an invasive procedure called adrenal vein sampling (AVS) in which small catheters are placed in each adrenal vein. However, this is time-consuming, technically demanding, and fails in 20-50% of cases. To address this, researchers have adopted a novel approach using PET-CT as an alternative to AVS. Currently, this uses a tracer called metomidate labelled with carbon-11 (11C MTO), which is taken up preferentially by the adrenal gland, and in particular by adrenal tumours causing PA. However, its utility is limited by a short half-life, which means the scan can only be performed in centres with a cyclotron facility (currently less than 10 NHS sites). The aim of this study is to investigate the safety of a new tracer with a longer half-life, [18F]CETO, that could be made available for use in many more centres.

Who can participate?
Healthy volunteers and patients with PA (patients with single adrenal gland involvement and where both adrenals are affected)

What does the study involve?
Healthy volunteers will have a single [18F]CETO PET-CT scan, while patients will undergo two [18F]CETO scans.

What are the possible benefits and risks of participating?
There is no anticipated benefit for healthy volunteers participating in this study. However, information collected as part of participation in this trial may benefit patients with primary aldosteronism in the future. Involvement in this study will require two visits to hospital, including a one-night stay. At each visit blood samples will be taken. Some participants may find this uncomfortable and bruising may occur at the site of the blood sample. Before the PET-CT

scan, a cannula will be placed in a vein, and this will be used for injecting the tracer into the blood. There may be local bruising following insertion of the cannula. The study will use a test called a short synacthen test to determine how the adrenal gland is functioning. This requires an injection with a chemical called synacthen. Immediately following injection of synacthen, some participants may report a warm sensation with flushing, and occasional nausea and light-headedness, which resolves within 1-2 minutes without the need for any treatment. The PET-CT scans in the trial are extra scans compared to if participants did not take part in the study. PET-CT scans use ionising radiation to form images of the body and provide doctors with other clinical information. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. All humans are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about 50% of people at some point in their life. Taking part in this trial will increase the chances of this happening by 0.02%.

Where is the study run from?
Cambridge University Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
April 2016 to November 2020 (updated 13/01/2021, previously: December 2020)

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2018-004851-18

IRAS number
248713

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 43841, IRAS 248713

Study information

Scientific Title
A Phase I clinical trial evaluating the safety and efficacy of up to two administrations of the adrenal PET tracer [18F]CETO in healthy volunteers and patients with primary aldosteronism

Acronym
CETO

Study objectives
[18F]CETO is a safe radiotracer when administered in either healthy volunteers or patients with primary aldosteronism.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 05/02/2020, London - West London & GTAC Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 104 8124; nrescommittee.london-westlondon@nhs.net), REC ref: 19/LO/1814

Study design
Non-randomised; Interventional; Design type: Diagnosis, Imaging

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Primary aldosteronism

Interventions
This study will investigate the administration of a small dose of a PET radiotracer in a single centre, with participants being made aware of the type of tracer being administered. The study is designed to assess the safety of administering small doses of [18F]CETO in up to 5 healthy volunteers and 6 patients with primary aldosteronism (PA). The number of participants that will be recruited represents a sufficient number to allow a first-in-human safety assessment of [18F] CETO administration. Recruitment of healthy volunteers and patients will occur concurrently (i.e. it will not be necessary for all healthy volunteers to be recruited before patients will be recruited).

Potential healthy volunteers will be recruited through a poster to be displayed within Cambridge University Hospitals NHS Foundation Trust and University of Cambridge premises in addition to word of mouth. Patients will be identified from the Endocrine Clinic at Cambridge University Hospitals NHS Foundation Trust and from endocrine referrals to Cambridge from neighbouring Trusts as per routine standard clinical practice. For logistical and safety reasons, no more than 2 participants will be recruited at once.

A participant information sheet will be provided for individuals expressing interest in the study. They will be invited for a screening visit in the Endocrine Investigation Unit (EIU), at least 24hrs after being provided with the information sheet, and having had the opportunity to ask any questions that they might have about the study. Potential participants who are interested in taking part will be required to provide written informed consent at the start of their screening visit. A photo ID check will be performed to verify potential participant's identity. Following this, a clinical assessment (which will include a full medical history and physical examination), blood sampling (15-20 ml, which is equivalent to approximately one tablespoon) including for

pregnancy where required, a urine drugs-of-abuse test and an adrenal function test known as a Short Synacthen Test (SST) will be performed. The SST is a test that is commonly used in routine endocrine practice, and involves taking a second blood sample approximately 30 minutes after injection of Synacthen 250 micrograms which stimulates cortisol production from the adrenal gland. The results from these assessments will be checked against the inclusion and exclusion criteria to confirm eligibility for involvement in the trial.

Following the screening visit, a member of the trial team will contact the participant's GP to verify their eligibility to be enrolled in the trial. Confirmation of the participant's relevant past medical and surgical history, current medications, recreational drug use, alcohol consumption, previous clinical trial involvement and previous radiation exposure will be verified with the GP. Written communication verifying participant eligibility will be sought from the participant's GP prior to proceeding to the baseline visit and PET-CT scan. All healthy volunteers will be registered on The Over-Volunteering Prevention System (TOPS) database, and any existing record of participants on the database will be reviewed prior to confirming their eligibility for this trial. On verification of eligibility, participants will be informed of their successful recruitment onto the trial by a member of the research team. A baseline visit will be booked with the participant.

Participants will attend the baseline assessment in the EIU, at least 7 days following the screening assessment, which will coincide with the day of the PET-CT scan. Participants will be asked to come fasting (for 4 hours, water permitted). A photo ID check will be performed in order to verify the participant's identity prior to dosing. Participants will have an updated clinical assessment with further blood tests (15-20 ml), a urine pregnancy test where required and insertion of a cannula into a vein. Participants will be accompanied by a member of the research team to the PET-CT unit where they will receive a short (lasting approximately 30 seconds) intravenous injection of a small volume of [18F]CETO, followed immediately by a PET-CT scan. The duration of the scan will be 90 minutes, during which participants will need to remain flat and stationary in the scanner. A member of the research team will be present during this time should the participant need to speak to them.

After completion of the scan, participants will remain in the PET-CT unit for approximately 4 hours after injection of the radiotracer. They will be monitored throughout this time by a trial research nurse and members of the PET-CT team, and will be reviewed on a regular basis by a clinical research fellow or the Principal Investigator. The unit is a fully accredited NHS PET facility and is fully equipped to deal with any adverse event following [18F]CETO administration. The unit contains a resuscitation trolley which contains equipment for use in the event of a clinical emergency and compliant with UK Resuscitation Council recommendations. At a minimum, all clinical members of the research team, in addition to PET/CT clinical staff members, are trained in providing basic life support. Therefore, they will be suitably qualified to use the available resuscitation equipment. Whilst on the PET-CT unit, vital signs will be checked at approximately 30-minute intervals throughout this time. Participants will subsequently be accompanied to the CLRF (which lies on the same hospital corridor as the PET-CT unit) by the clinical research fellow and research nurse, where they will be observed in the Early Phase Unit of the Clinical Research Facility (CLRF) until approximately 24 hours after the injection of [18F]CETO. On arrival at the CLRF, vital signs will be checked and repeated when clinically indicated thereafter.

A clinical member of the research team will be available throughout the duration of the participant's stay. They will be able to attend the CLRF to review the participant within approximately 10 minutes of a request for clinical review by the CLRF nursing team. In the unlikely event that the participant acutely deteriorates, a CUH rapid response team will attend the CLRF and make a decision regarding transfer to the main hospital. The Early Phase unit is on

Level 3 of the CLRF, with a link corridor to allow direct access to the main hospital. It takes approximately 2 minutes for participants to be transferred to the intensive care unit in the rare instance that this situation arises.

On the morning following the scan, participants will undergo repeat blood tests and an SST (10 ml, approximately half a tablespoon) to confirm expected adrenal function. Following a review of the blood test results by a clinical member of the research team, participant's will be discharged from the CLRF. Discharge from the CLRF is expected to occur approximately 24 hours after the injection of [18F]CETO.

In the unlikely event of an abnormal SST result the morning after [18F]CETO administration, a decision will be made to determine whether participants require a temporary low-dose steroid replacement regimen. Additionally, any participants with an abnormal SST will be invited to a follow-up visit at 7 days (+/-2 days) following the PET-CT scan for a repeat SST. In the extremely unlikely event that the abnormality persists, the patient's care will be transferred to the Endocrine Clinic at CUH for ongoing management and, in parallel, continued follow up will be undertaken by the research team as clinically indicated. Patients who return an abnormal SST following the initial PET-CT scan will not undergo a repeat PET-CT scan.

Patients (but not healthy volunteers) will undergo a repeat PET-CT scan a minimum of 7 days following the initial PET-CT scan. Patients will receive a low-dose Dexamethasone regime prior to the scan (500 micrograms 4 times a day for 3 days before the scan) which is part of standard clinical care. Patients will be required to complete a medication diary to track their self-administration. During the visit, a photo ID check will be again be performed to confirm the participant's identity. Blood samples will be taken (15-20 ml) and another urine pregnancy test will be performed where required. Following the repeat [18F]CETO administration and PET-CT scan, patients will be observed for up to 4 hours in the PET-CT unit (vital signs will be recorded and repeated approximately every 30 minutes by a member of the research team), after which they will be allowed to return home. There will not be a routine requirement for admission to the CLRF following the repeat scan.

PET-CT scans will be assessed and reported by a consultant radiologist approximately 24-48 hours following the scan.

Intervention Type
Other

Phase
Phase I

Primary outcome measure
Safety of [18F]CETO measured according to the frequency of adverse events, serious adverse events, clinically significant changes in vital signs, ECG and laboratory sampling; assessed at the conclusion of trial participation

Secondary outcome measures
1. [18F]CETO uptake by the adrenal glands assessed by measurement of Standardized Uptake Values (SUV) over the left and right adrenal glands: all assessments will be performed by a dedicated blinded reviewer; assessed at each of up to two PET-CT scans

2. Adrenal uptake of [18F]CETO in bilateral versus unilateral cases of PA performed by comparing SUV values of both adrenal glands in three patients with each subtype of PA (using a dedicated blinded reviewer); assessed at each of up to two PET-CT scans

Overall study start date
01/04/2016

Completion date
20/11/2020

Eligibility

Key inclusion criteria
Healthy volunteers:
To be included in the trial the participant must:
1. Give written informed consent
2. Be aged 50 years or over
3. Have no underlying medical conditions
4. Be able to lie down for at least 2 hours and not be claustrophobic

In addition, all female participants must be:
1. Post-menopausal (no menses for 12 months, without an alternative medical cause)

Patients:
To be included in the trial the patient must:
1. Give written informed consent
2. Be aged 40 years or over
3. Be able to lie down for at least 2 hours and not be claustrophobic
4. Fulfil the following criteria:
4.1. Have a confirmed diagnosis of PA as per Endocrine Society guidelines*
4.2. Have undergone successful lateralisation of the cause of PA to one or both adrenal glands by adrenal vein sampling (AVS).
4.3. Be willing to have two scans

In addition, all female patients must have a negative (blood) pregnancy test at the screening visit

*Endocrine Society guidelines are:
1. At least one paired measurement of plasma renin and aldosterone, measured off Spironolactone/Eplerenone within past 12 months, showing ARR above local threshold value
2. One of the following two criteria:
2.1. Plasma aldosterone > 190 pmol/L following saline infusion
2.2. Spontaneous hypokalaemia, suppressed plasma renin and plasma aldosterone > 550 pmol/L

Participant type(s)
Mixed

Age group
Adult

Sex
Both

Target number of participants
Planned Sample Size: 11; UK Sample Size: 11

Key exclusion criteria
All participants:
1. Allergy to radiographic contrast agents
2. Allergy or contraindication to synacthen
3. Pregnancy, breastfeeding, or the intention to become pregnant during the 6 months following trial participation
4. Positive pregnancy test at the screening or baseline visits
5. Assessed by the investigator as being unable or unwilling to comply with the requirements of the study protocol.
6. Receipt of another IMP as part of a CTIMP
7. Prior radiation exposure as part of previous research studies
8. Recreational drug use, or substance/alcohol dependency
9. Clinically abnormal screening blood tests [including abnormal short synacthen test]

Additional exclusion criteria for healthy volunteers:
1. Women of child-bearing potential (i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy)
2. Exposure to radiation during their work
3. Received more than 10 mSv of radioactivity in the past 12 months
4. Any subject with a history of adrenal disease or who, at the screening visit, reports symptoms, or exhibits physical signs, that could be consistent with previously unsuspected adrenal disease

Additional exclusion criteria for patients:
1. Allergy or contraindication to dexamethasone treatment (or lactose intolerant)

Date of first enrolment
10/03/2020

Date of final enrolment
17/11/2020

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Addenbrooke's Hospital
Hills Road

Cambridge
United Kingdom
CB2 0QQ

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

Sponsor details
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Sponsor type
Hospital/treatment centre

Website
http://www.cuh.org.uk/

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council; Grant Codes: MR/P01710X/1

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The researchers would anticipate presenting the findings at scientific meetings in addition to publication in a high-impact peer-reviewed journal.

Intention to publish date
31/12/2021

Individual participant data (IPD) sharing plan
As this study is First in Human with only a small number of participants, the researchers anticipate that there is likely to be limited value in sharing the datasets generated during and/or analysed following the current study.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v1.1	19/12/2019	19/05/2020	No	Yes
Participant information sheet	version v1.1	19/12/2019	19/05/2020	No	Yes
Protocol file	version v1.2	19/12/2019	19/05/2020	No	No
HRA research summary			28/06/2023	No	No