ISRCTN59912845 https://doi.org/10.1186/ISRCTN59912845

A study in healthy male volunteers to look at how the radiolabeled test medicine ([14C] encaleret) is taken up, broken down and removed by the body

Submission date
31/01/2023

Recruitment status
No longer recruiting

Registration date
20/03/2023

Overall study status
Completed

Last Edited
21/12/2023

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
The Sponsor is developing the test medicine, encaleret, for the potential treatment of a rare genetic disorder - autosomal dominant hypocalcaemia type 1 (ADH1), which occurs in around 1 in 70,000 people. ADH1 is caused by a genetic mutation, resulting in decreased release of parathyroid hormone from the parathyroid glands and decreased urine calcium reabsorption in the kidneys. This results in excessive calcium excretion in the urine, which can lead to kidney stones/calcifications, impaired kidney function, and low calcium and magnesium blood levels, which has heart and nerve effects, such as heart rhythm abnormalities, seizures, and muscle spasms and cramps.
This single part healthy volunteer study will try to identify how the test medicine is taken up, broken down and removed from the body. To help investigate this, the test medicine is radiolabelled meaning that the test medicine has a trace amount of radioactive component (carbon-14; also referred to as 14C) which helps us track where the test medicine is in the body. This study will also try to identify the safety and tolerability of the test medicine, as well as evaluate how it tastes.

Who can participate?
This study will take place at one non-NHS site, enrolling up to 8 male volunteers aged between 40 and 65 years.

What does the study involve?
On Day 1, up to 8 volunteers will receive a single oral dose of the radiolabelled test medicine with an empty stomach. Volunteer's blood, urine and faeces will be taken throughout the study for analysis of the test medicine and for their safety. Volunteers will remain in the clinical unit until Day 8, however if required levels of radioactive recovery (amount of radioactive component [14C] retrieved in the urine and faeces) have not been met, they may be required to remain at the clinical unit until Day 12. If relevant criteria have not been met at this point, home collections of urine and/or faeces may be required.

Volunteers are expected to be involved in this study for approximately 6 weeks from screening to conclusion of the study.

What are the possible benefits and risks of participating?
Benefits:
No known medical benefit from taking test medicine, however development of a treatment for autosomal dominant hypocalcaemia type 1 may benefit those individuals suffering from it.
Risks:
1. As this is a Phase I study, the most relevant population is healthy volunteers. It is considered that the risk/benefit evaluation in this study supports the use of healthy volunteers. There is always a risk that the stipend in healthy volunteer studies could represent coercion. The time spent in the clinic, travel, inconvenience and other expenses factor in calculating the stipend. Perception of risk is not considered in this calculation.
2. When investigating new medicines there is always a risk of unexpected side effects and occasionally allergic reactions. Volunteers will be closely monitored during the study.
3. Volunteers may experience side effects from the test medicine in this study. Known side effects include but not limited to: constipation, headache, muscular pain, dizziness, nausea, blood in urine and common cold. Full information on possible side effects is provided to volunteers in the Participant Information Sheet and Informed Consent Form.
4. There will be an extended period of fasting for the volunteers taking part in this study. Volunteers will have an evening snack the night before dosing, and then will only be allowed water until 4 hours post-dose, at which point lunch will be provided. Water will be allowed freely after 1 hour post-dose. Volunteers will be monitored for signs of dehydration and fatigue.
5. During the study, study staff will perform some tests early in the morning or during the night. Volunteers may be on a ward with up to 20 other people which could mean that the sleep could be interrupted.
6. Blood samples will be collected during the study. Collection of these samples can cause soreness and bruising of the arms but these problems usually clear up within a few days to a few weeks.
7. ECG stickers on volunteers' chests and limbs may cause some local irritation and may be uncomfortable to remove but volunteers will be closely monitored to ensure any local irritation does not persist.
8. If a volunteer has private medical insurance, it is advised to check with the company if taking part in the study is considered a ‘material fact’ that should be reported to the insurance company before agreeing to take part in this study. This is to ensure that taking part in the study will not affect medical insurance.
9. By taking part in the study the volunteers will be exposed to a small amount of radiation. The effective radiation dose that each volunteer will receive in total will not exceed 1.0 mSv. This is approximately 4.5 months of the average radiation exposure received in the UK each year (2.7 mSv). This equates to slightly more than the radiation dose that would result from 2 abdominal x- rays (0.47 mSv each).
10. Due to the phototoxic data for encaleret, volunteers will be advised to minimise exposure to sunlight by spending a reduced amount of time outdoors/remaining inside the clinical unit during the residential period of the study, wearing sunglasses and clothing that minimises exposure to sunlight and using sun cream on exposed areas when going outdoors. They will also be advised not to use sunbeds. This restriction will be advised from dosing until discharge from the clinical unit.

Where is the study run from?
Quotient Sciences Limited (UK)

When is the study starting and how long is it expected to run for?
January 2023 to April 2023

Who is funding the study?
Calcilytix Therapeutics, Inc., a BridgeBio Company (USA)

Who is the main contact?
Scott Adler, scott.adler@bridgebio.com

Contact information

Type(s)
Public

Contact name
Dr Gustavo Lorente

Contact details
1800 Owens Street
Suite C-1200
San Francisco
United States of America
CA 94158
-
Gustavo.lorente@calcilytix.com

Type(s)
Principal investigator

Contact name
Dr Philip Evans

Contact details
Mere Way
Ruddington Fields
Nottingham
United Kingdom
NG11 6JS
+44 330 3031000
recruitment@weneedyou.co.uk

Type(s)
Scientific

Contact name
Dr Scott Adler

Contact details
1800 Owens Street
Suite C-1200

San Francisco
United States of America
CA 94158
-
scott.adler@bridgebio.com

Additional identifiers

Integrated Research Application System (IRAS)
1006991

Protocol serial number
CLTX-305-101, QSC205855

Study information

Scientific Title
An open label, single-dose, single-period study designed to assess the mass balance recovery, metabolite profile and metabolite identification of [14C]encaleret in healthy male subjects

Study objectives
Primary objectives:
1. To assess the mass balance recovery (how much radioactivity can be recovered from the urine and faeces) after a single oral dose of [14C]encaleret.
2. To provide plasma, urine and faecal samples for metabolite (breakdown product) profiling and structural identification.

Secondary objectives:
1. To determine the routes and rates of elimination of [14C]encaleret.
2. To identify the chemical structure of each metabolite accounting for more than 10% of circulating total radioactivity or accounting for 10% or more of the dose in excreta.
3. To further explore the oral pharmacokinetics (what the body does to the test medicine; PK) of encaleret.
4. To evaluate the extent of distribution of total radioactivity into blood cells.
5. To provide additional safety and tolerability information for encaleret.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 22/03/2023, Wales REC 2 (Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, United Kingdom; +44 7920 565664; Wales.REC2@wales.nhs.uk), ref: 23/WA/0008
2. Approved 22/03/2023, MHRA (10 South Colonnade, Canary Wharf, London, E14 4PU, UK; +44 (0)20 3080 6000; info@mhra.gov.uk)

Primary study design
Interventional

Study design
Interventional non-randomized

Study type(s)
Other

Health condition(s) or problem(s) studied
Autosomal dominant hypocalcaemia type 1 (ADH1)

Interventions
Participants will receive a single oral administration of 54 mg [14C]encaleret Oral Solution containing not more than (NMT) 3.7 megabecquerel (MBq) 14C in the fasted state.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
[14C]encaleret Oral Solution

Primary outcome(s)
1. Mass balance recovery of total radioactivity in all excreta (urine and faeces): CumAe and Cum% Ae.
2. Collection of plasma, urine and faeces samples for metabolite profiling, structural identification, and quantification analysis of encaleret metabolites.
The timepoints will be evaluated from collection of urine and faeces from pre-dose on Day 1 until a maximum of 264 hours post-dose (Day 12) in the clinical unit, home collections may be required after this time. Plasma samples will be collected from Day 1 to Day 12.

Key secondary outcome(s)
1. Determination of routes and rates of elimination of [14C]encaleret by calculation of Ae, %Ae, CumAe and Cum%Ae for total radioactivity by interval in all excreta (urine and faeces).
2. Identification of the chemical structure of each metabolite accounting for more than 10% by area under the curve (AUC) of circulating total radioactivity or accounting for 10% or more of the administered radioactive dose in excreta (urine and faeces). Collection of urine and faeces from pre-dose on Day 1 until a maximum of 264 hours post-dose (Day 12) in the clinical unit, home collections may be required after this time.
3. PK parameters for encaleret, its metabolites, M1 and M3, and total radioactivity in plasma following a single oral dose of encaleret, including but not limited to the following as applicable: Tmax, Cmax, AUC(0-last), AUC(0-inf), T1/2 and metabolite ratios taken from pre-dose on Day 1 to 168 hours post-dose (Day 8)
4. Evaluation of whole blood: plasma concentration ratios for total radioactivity taken from pre-dose on Day 1 to 168 hours post-dose (Day 8)
5. To provide additional safety and tolerability information for encaleret by assessing incidence of AEs, physical examinations and change from baseline for vital signs, ECGs, and laboratory safety tests from screening to discharge (Day 12 maximum)

Completion date
27/04/2023

Eligibility

Key inclusion criteria
1. Must provide written informed consent
2. Must be willing and able to communicate and participate in the whole study
3. Must be willing to consume the drug dose, which contains a small amount of alcohol and is radiolabelled with 14C
4. Aged 40 to 65 years inclusive at the time of signing informed consent
5. Must agree to adhere to the contraception requirements defined in the clinical protocol
6. Healthy males as assessed by the investigator
7. Body mass index (BMI) of 18.0 to 35.0 kg/m² as measured at screening
8. Must have regular bowel movements (i.e. average stool production of ≥1 and ≤3 stools per day)

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
Male

Key exclusion criteria
1. Serious adverse reaction or serious hypersensitivity to any drug or formulation excipients
2. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hay fever is allowed unless it is active
3. History of clinically significant cardiovascular, renal, hepatic, dermatological, chronic respiratory or GI disease (especially peptic ulceration, GI bleeding, ulcerative colitis, Crohn's Disease or Irritable Bowel Syndrome), neurological or psychiatric disorder, as judged by the investigator
4. History of GI surgery (with the exception of appendectomy unless it was performed within the previous 12 months)
5. Acute diarrhoea or constipation in the 7 days before the predicted Day 1. If screening occurs >7 days before the Day 1, this criterion will be determined on Day 1. Diarrhoea will be defined as the passage of liquid faeces and/or a stool frequency of greater than 3 times per day. Constipation will be defined as a failure to open the bowels more frequently than every other day
6. Subject has a medical condition that may adversely affect taste or smell activity including but not limited to mouth ulcers, significant gum disease, and respiratory and/or sinus infection or cold
7. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening
8. Evidence of current SARS-CoV-2 infection within 4 weeks of IMP administration
9. Clinically significant abnormal clinical chemistry, haematology or urinalysis as judged by the investigator. Subjects with Gilbert's Syndrome are allowed

10. Subjects with corrected Ca above the upper limit of the normal reference range
11. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) 1 and 2 antibody results
12. Evidence of renal impairment at screening, as indicated by an estimated creatinine clearance (CLcr) of <80 mL/min using the Cockcroft-Gault equation
13. Subjects who have received any IMP in a clinical research study within the 90 days prior to Day 1, or less than 5 elimination half-lives prior to Day 1, whichever is longer
14. Radiation exposure, including that from the present study, excluding background radiation but including diagnostic x-rays and other medical exposures, exceeding 5 mSv in the last 12 months or 10 mSv in the last 5 years. No occupationally exposed worker, as defined in the Ionising Radiation Regulations 2017, shall participate in the study
15. Donation of blood or plasma within the previous 3 months or loss of greater than 400 mL of blood
16. Subjects who are taking, or have taken, any prescribed or over-the-counter medication or herbal remedies (other than up to 4 g of paracetamol per day) in the 14 days before IMP administration. COVID-19 vaccines are accepted concomitant medications up to 72 h before dosing. Exceptions may apply, as determined by the investigator, if each of the following criteria are met: medication with a short half life if the washout is such that no pharmacodynamic activity is expected by the time of dosing with IMP; and if the use of medication does not jeopardise the safety of the trial subject; and if the use of medication is not considered to interfere with the objectives of the study
17. Subjects who have had a COVID-19 vaccine within 72 h before dosing
18. History of any drug or alcohol abuse in the past 2 years
19. Regular alcohol consumption in males >21 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type)
20. A confirmed positive alcohol breath test at screening or admission
21. Current smokers and those who have smoked within the last 12 months
22. A confirmed breath carbon monoxide reading of greater than 10 ppm at screening or admission
23. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
24. Confirmed positive drugs of abuse test result
25. Male subjects with pregnant or lactating partners
26. Subjects who are, or are immediate family members of, a study site or sponsor employee
27. Failure to satisfy the investigator of fitness to participate for any other reason

Date of first enrolment
28/03/2023

Date of final enrolment
27/04/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Quotient Sciences Limited
Mere Way
Ruddington Fields
Nottingham
United Kingdom
NG11 6JS

Sponsor information

Organisation
Calcilytix Therapeutics, Inc., a BridgeBio Company

Funder(s)

Funder type
Industry

Funder Name
Calcilytix Therapeutics, Inc., a BridgeBio Company

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to commercial sensitivity.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			20/09/2023	No	No