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Treatment of patients with Fahr's disease or syndrome with Etidronate

Submission date
16/11/2024

Recruitment status
Recruiting

Registration date
06/02/2025

Overall study status
Ongoing

Last Edited
17/02/2026

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
Fahr's disease and syndrome are rare disorders leading to calcification of the small arteries in deep regions of the brain (basal ganglia), resulting in a wide range of symptoms, including cognitive decline, movement disorders and neuropsychiatric symptoms. No cure is available. Studies have shown the potential of treatment of these abnormal vascular calcifications with bisphosphonates, a group of medications used to treat osteoporosis and similar diseases. The aim of this study is to evaluate the effects of etidronate during 12 months of follow-up in patients with Fahr's disease or syndrome.

Who can participate?
Patients aged 18 years and over with Fahr's disease or syndrome.

What does the study involve?
Etidronate and placebo are administered in capsules daily for 2 weeks on followed by 10 weeks off. Cognitive functioning, mobility, neuropsychiatric symptoms, volume of brain calcifications, dependence in activities of daily living, and quality of life are all measured after 12 months of treatment.

What are the possible benefits and risks of participating?
Etidronate may reduce symptoms of Fahr’s disease, but that is not certain. At the moment, there are no curative treatment options for Fahr's disease. Participating in this study is of great scientific value: it helps to find treatment options for this disease, for yourself and for future patients.

Where is the study run from?
1. University Medical Center Utrecht (The Netherlands)
2. University College London Hospital (UK)

When is the study starting and how long is it expected to run for?
April 2023 to December 2027

Who is funding the study?
1. University Medical Center Utrecht (The Netherlands)
2. Dutch Brain Foundation (The Netherlands)

Who is the main contact?
1. Dr Amit Batla, a.batla@ucl.ac.uk
2. Dr Huiberdina Koek, h.l.koek@umcutrecht.nl

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Scientific, Principal investigator, Public

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05662111

Clinical Trials Information System (CTIS)
2022-003299-17

Integrated Research Application System (IRAS)

1009530

Protocol serial number
22-1005-CALCIFADE

Study information

Scientific Title
A randomized, placebo-controlled, double-blind trial to study the effects of Etidronate on ectopic CALCIfication in FAhr’s Disease or syndrome: the CALCIFADE trial

Acronym
CALCIFADE

Study objectives
The primary objective is to determine whether etidronate can halt or attenuate the deterioration of cognitive functioning in patients with Fahr’s disease or syndrome.

The secondary objectives are to determine:
1. Whether etidronate can halt or attenuate deterioration of mobility, psychiatric problems, dependence in activities of daily living, and quality of life in patients with Fahr’s disease or syndrome.
2. Whether etidronate leads to stabilization or attenuation of ongoing calcification in the brain as quantified by CT imaging in patients with Fahr’s disease or syndrome.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. Approved 20/03/2023, Medical Research Ethics Committee NedMec (Heidelberglaan 100, Utrecht, 3584 CX, Netherlands; +31 88 7556376; metc@nedmec.nl), ref: 22-1005/Gm-G

2. Approved 04/02/2025, London - Central Research Ethics Committee (3rd Floor 3 Piccadilly Place, London Road, Manchester, M1 3BN, United Kingdom; +44 207 104 8282; londoncentral.rec@hra.nhs.uk), ref: 24/LO/0870

Primary study design
Interventional

Study design
Interventional double-blind randomized parallel group placebo-controlled trial

Study type(s)
Efficacy

Health condition(s) or problem(s) studied
Patients with symptoms attributable to Fahr's disease or Fahr's syndrome (brain calcifications)

Interventions

Patients will be randomized 1:1 to daily, oral, etidronate 400 mg capsules 20 mg/kg for 2 weeks on followed by 10 weeks off during 1 year, or an identical product without the active pharmacological substance (placebo) in the same cyclical regimen.

Randomisation will be performed using block randomisation with variable block sizes by the Clinical Drug Research Unit of UMCU, the Netherlands, in agreement with the study protocol.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Etidronate disodium

Primary outcome(s)
1. Overall cognitive functioning is measured using Montreal Cognitive Assessment (MoCA; range 0-30, higher scores mean better outcome) at baseline and 12 months
2. Memory is measured using composite z-score of Rivermead Behavioral Memory Test (RBMT) Stories immediate and delayed recall, Rey complex figure test immediate and delayed recall at baseline and 12 months
3. Attention and speed of information processing is measured using composite z-score of Wechsler Adult Intelligence Scale third edition (WAIS-III) Digit Span Forward, Trail Making Test A (TMT-A), Stroop I and II at baseline and 12 months
4. Executive functioning is measured using composite z-score of Wechsler Adult Intelligence Scale third edition (WAIS-III) Digit Span Backward, Trail Making Test B (TMT-B), Stroop III, semantic and letter fluency at baseline and 12 months
5. Social cognition is measured using Facial Expressions of Emotion - Stimuli and Tests (FEEST; scored based on normative data) at baseline and 12 months

Key secondary outcome(s)
1. Mobility is measured using the condensed version of the Balance Evaluation Systems Test (Mini-BESTest; range 0-28, higher scores mean better outcome) at baseline and 12 months
2. Mobility is measured using the Unified Parkinson's Disease Rating Scale, part III (UPDRS; range 0-56, higher scores mean worse outcome) at baseline and 12 months
3. Neuropsychiatric symptoms are measured using the Neuropsychiatric Inventory (NPI; range 0-144, higher scores mean worse outcome) at baseline and 12 months
4. Activities of daily living are measured using the Katz-15 scale (range 0-15, higher scores mean worse outcome) at baseline and 12 months
5. Quality of life is measured using the 36-item Short Form Health Survey (SF-36; range 0-100, higher scores mean better outcome) at baseline and 12 months
6. Brain calcification volume is measured using the volume of calcification quantified in computed tomography scan (milliliters) at baseline and 12 months

Completion date
31/12/2027

Eligibility

Key inclusion criteria

1. Age of 18 years or over
2. Clinical diagnosis of Fahr's disease or syndrome. No international accepted diagnostic criteria for Fahr's disease or syndrome exist yet. It is diagnosed mostly based on the clinical presentation. For the present study the following criteria are used:
2.1. Clinical symptoms consistent with a clinical diagnosis of Fahr's disease or syndrome.
2.2 Bilateral calcifications of the basal ganglia as seen on the computed tomography (CT) scan of the head. To rule out basal ganglia calcifications due to aging, a CT based calcification score will be used as proposed by Nicolas et al. Calcification is graded from 0 (no calcification) to 5 (serious and confluent) in specific locations of the brain; lenticular, caudate, thalamus nuclei, subcortical white matter, cortex, cerebellar hemispheres, vermis, midbrain, pons, and medulla. The total calcification score (ranging from 0 to 80) is obtained by adding all location-specific points, where a score higher than the age-specific threshold points at Fahr's disease or syndrome.
3. Furthermore, the next criteria are supportive for the clinical diagnosis of PFBC:
3.1. Frequently, the family history is consistent with autosomal dominant inheritance. A positive family history with at least one relative in the first or second degree with symptoms of PFBC is supportive for the clinical diagnosis of PFBC.
3.2. The presence of a (likely) pathogenic mutation in one of the PFBC-related genes is supportive for the clinical diagnosis of PFBC. Mutations in up to now 4 known genes are associated with an autosomal dominant pattern of inheritance: solute carrier family 20 member 2 (SLC20A2) (OMIM#213600), xenotropic and polytropic retrovirus receptor 1 (XPR1) (OMIM#616413), platelet-derived growth factor b (PDGFB) (OMIM#615483), and platelet-derived growth factor receptor b (PDGFRB) (OMIM#615007). Autosomal recessively inherited PFBC is associated with mutations in two genes: myogenesis-regulating glycosidase (MYORG) (OMIM#618317) and junctional adhesion molecule 2 (JAM2) (OMIM#618824).

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Unable or unwilling to sign an informed consent
2. Severe renal impairment (estimated glomerular filtration rate (eGFR) of <30 ml/min/1.73m² calculated using CKD-EPI equation)
3. Contraindication to receiving oral medication (for example severe dysphagia)

4. Known abnormality of the oesophagus that would interfere with the passage of the drug (for example oesophageal strictures or achalasia)
5. Known sensitivity to etidronate
6. Pregnancy, women with an active pregnancy wish <1 year, or women who are breastfeeding at the time of inclusion
7. Inability to undergo an English neuropsychological assessment (for example, non-fluent English speakers or severe visual, hearing or motor impairment)
8. Any other medical or social condition that puts the subject at risk of harm during the study or might adversely affect the interpretation of the study data
9. Use of bisphosphonates during the last 5 years
10. Hypocalcaemia (calcium <2.20 mmol/L)
11. 25-OH vitamin D deficiency <35 nmol/L
After correction of hypocalcaemia or vitamin D deficiency, a participant is again suitable for participation

Date of first enrolment
03/04/2023

Date of final enrolment
31/12/2026

Locations

Countries of recruitment
United Kingdom

England

Netherlands

Study participating centre
Uclh
250 Euston Road
London
England
NW1 2PQ

Study participating centre
University Medical Center Utrecht
Heidelberglaan 100
Utrecht
Netherlands
3584 CX

Sponsor information

Organisation
University Medical Center Utrecht

ROR
https://ror.org/0575yy874

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Universitair Medisch Centrum Utrecht

Alternative Name(s)
UMC Utrecht, University Medical Center Utrecht, UMCU, UMC

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
Netherlands

Funder Name
Dutch Brain Foundation

Results and Publications

Individual participant data (IPD) sharing plan
Researchers can contact the scientific point of contact for access to the datasets (Birgitta Snijders, b.m.g.snijders@umcutrecht.nl) for access to the datasets. The type of data that will be shared depends on the request. The informed consent form includes the question whether patients give consent to store and reuse their data for other research projects. Patients can indicate whether they agree to this or not. Data will be shared pseudonymized. Only data that is necessary to answer the specific research question, will be shared upon request, since data might be retraceable to an individual person.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		07/04/2024	18/03/2025	Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes