

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

Submission date 16/11/2024	Recruitment status Recruiting	<input type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 06/02/2025	Overall study status Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 20/03/2025	Condition category Nervous System Diseases	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> 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 2026

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 Birgitta Snijders, b.m.g.snijders@umcutrecht.nl
2. Dr Amit Batla, a.batla@ucl.ac.uk
3. Dr Huiberdina Koek, h.l.koek@umcutrecht.nl

Study website

<https://www.umcutrecht.nl/nl/wetenschappelijk-onderzoek/calcifade-studie?lang=en>

Contact information

Type(s)

Public, Scientific

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Additional identifiers**EudraCT/CTIS number**

2022-003299-17

IRAS number

1009530

ClinicalTrials.gov number

NCT05662111

Secondary identifying numbers

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

Study design

Interventional double-blind randomized parallel group placebo-controlled trial

Primary study design

Interventional

Secondary study design

Randomised parallel trial

Study setting(s)

Hospital

Study type(s)

Efficacy

Participant information sheet

Not available in web format, please use the contact details to request a participant information sheet

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

Pharmaceutical study type(s)

Therapy

Phase

Phase II

Drug/device/biological/vaccine name(s)

Etidronate disodium

Primary outcome measure

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

Secondary outcome measures

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

Overall study start date

03/04/2023

Completion date

31/12/2026

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

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

98

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

31/12/2025

Locations

Countries of recruitment

England

Netherlands

United Kingdom

Study participating centre

Uclh

250 Euston Road

London

United Kingdom

NW1 2PQ

Study participating centre

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Sponsor information

Organisation

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Sponsor type

Hospital/treatment centre

Website

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ROR

<https://ror.org/0575yy874>

Funder(s)

Funder type

Hospital/treatment centre

Funder Name

Universitair Medisch Centrum Utrecht

Alternative Name(s)

UMC Utrecht, UMC

Funding Body Type

Private sector organisation

Funding Body Subtype

Universities (academic only)

Location

Netherlands

Funder Name

Dutch Brain Foundation

Results and Publications

Publication and dissemination plan

Peer reviewed scientific journals

Internal report

Conference presentation

Publication on website

Other publication

Submission to regulatory authorities

Intention to publish date

31/12/2027

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