DEnosumab for the treatment of FIbrous Dysplasia/McCune-Albright Syndrome in adults (DeFiD): a randomized double-blind placebo-controlled trial

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This study has been transitioned to CTIS with ID 2024-511090-30-00 check the CTIS register for the current data. To investigate whether 3 monthly Dmab will improve the clinical, radiological and biochemical manifestations of FD bone lesions.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Interventional

Summary

ID

NL-OMON53469

Source
ToetsingOnline

Brief title
DeFiD

Condition

- Musculoskeletal and connective tissue disorders congenital
- Musculoskeletal and connective tissue disorders congenital

Synonym
Fibrous Dysplasia/McCune Albright syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Stichting Dioraphte

Intervention

Keyword: bone turnover, Denosumab, fibrous dysplasia

Outcome measures

Primary outcome

The effect of Dmab on pain, assessed by the difference in maximum pain score after 6 months (2 injections) by Brief Pain Inventory

Secondary outcome

• to evaluate the effect of Dmab on average pain scores after 3, 6 months of treatment and in case of open label treatment after 9 and 12 months

• to evaluate the number of patients with 50% reduction of maximal pain (BPI) after 3, 6 months of treatment and in case of open label treatment after 9 and 12 months

• to evaluate the effect of Dmab on quality of life, assessed with questionaries (SF-36) at baseline, 3 months and after 6 months and in case of open label treatment after 9 and 12 months

• to evaluate the effect of Dmab on average weekly pain assessed through a pain diary with VAS score

• to investigate the effect of Dmab on Physical activity assessment (Health Assessment Questionnaire - Disability Index and screenshot of pedometer of activity during the last week on smartphone) measured at baseline, 3 months and 6 months, and in case of open label treatment after 9 and 12 months

• to evaluate the prevalence of possible neuropathic component of the reported pain through Pain Detect questionnaire

• to investigate the number of analgesics use and dosage used at baseline, 3 months and 6 months and in case of open label treatment after 9 and 12 months

• to assess the effect of Dmab on disease activity through laboratory measurements of bone markers at baseline, 3 months and 6 months, and in case of open label treatment after 9 and 12 months

• to assess the effect of Dmab on lesions activity and lesions size through bone scans at baseline and after 6 months, and in the case of open label treatment after 12 months

• to assess disease quantification by nuclear imaging before and after treatment (Skeletal Burden Score (SBS)

• to assess bone density and the presence of vertebral fractures (Dual-energy X-ray absorptiometry (DXA) + Vertebral Fractures Assessment (VFA) at baseline and after 12 months

• to assess potential side effects in the form of Atypical femoral fractures by performing and extended DXA after 12 months

Study description

Background summary

Fibrous dysplasia (FD) is a rare genetic disorder, caused by a post-zygotic mutation of the GNAS-gene, characterized by local replacement of bone by fibrous tissue in one (monostotic) or several bones (polyostotic). FD lesions can be associated with endocrinopathies or café au lait patches in the McCune-Albright syndrome (MAS), therefore the disease is termed FD/MAS. Bone lesions can lead to pain and low quality of life (QoL) and higher disease

burden is correlated with more pain and worse QoL. There is no cure for FD/MAS and while several treatments attempt to alleviate pain, current therapies failed to demonstrate any effect on pain, functional parameters, imaging aspect or disease progression. However, the RANKL-inhibitor Denosumab (Dmab) has emerged as a possible treatment, showing promising result in mouse models and in observational studies on the off label use in patients. As a clinical, biochemical and radiological response to Dmab has been observed in observational, non-randomized and non-controlled studies, the next step is to conduct a randomized, double-blind, controlled trial (RCT) comparing the effects of Dmab treatment with placebo in adult symptomatic patients with FD/MAS.

Study objective

This study has been transitioned to CTIS with ID 2024-511090-30-00 check the CTIS register for the current data.

To investigate whether 3 monthly Dmab will improve the clinical, radiological and biochemical manifestations of FD bone lesions.

Study design

double-blind placebo controlled 6 months intervention study followed by a 6 months open-label study

Intervention

Eligible patients will be randomized to treatment with either subcutaneous Dmab 120mg or placebo at baseline and 3 months in a blinded fashion. At 6 months, after 2 injections, patients with pain score <4 will exit the study to discontinue study medication and proceed in usual care, while patients with pain score >=4 or lesional growth will be offered Dmab 120 mg at 6 and 9 months in an open-label design.

Study burden and risks

The patient burden will be minimal, consisting of completing the study procedures at established time points and participating in a placebo controlled study. The collection of blood samples, physical examination and the completion of questionnaires requires engagement, however these procedures are already incorporated in standard care at our center, and a combined Na18F-PET-CT-scan will also be performed at baseline, at 6 months and at the end of study. Risks for AEs and for a rebound phenomenon after withdrawal from Dmab exist, although risks are minimalized by dental screening and close observation during the study phase and the current standard of care after discontinuing Dmab.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Being symptomatic with an established diagnosis of FD/MAS and closed growth plates (>18 years)
- Pain in the region of an FD localization, not responding to adequate pain treatment and
without mechanical component e.g. impending fracture
- Pain score from FD lesion for maximum or average pain on VAS >= 4
- Increased lesional activity defined as increased bone turnover markers (ALP, P1NP or CTX) or increased activity on Na[18F]-PET/CT or bone scintigraphy in at least one lesion
- Normal levels of calcium, parathyroid hormone and vitamin D (supplementation is allowed)
- Treated hypophosphatemia (defined as >0.7 at two separate measures)

- good dental health (last check within the last 12 months)

Exclusion criteria

- Active pregnancy wish, pregnancy or nursing
- Pain not related to FD
- Uncontrolled endocrine disease
- Untreated vitamin D deficiency, hypocalcemia or hypophosphatemia
- Previous use of bisphosphonates or Dmab < 6 months before inclusion (*6 months wash out*)
- Previously reported side effects on Dmab
- Inability to fulfil study requirements
- Poor untreated dental health without intention to get treatment
- Treatment with other bone influencing drugs, such as high doses corticosteroids

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-06-2023
Enrollment:	82
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Xgeva
Generic name:	Denosumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	24-03-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	12-06-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	07-03-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-511090-30-00
EudraCT	EUCTR2022-002611-29-NL
CCMO	NL82050.058.22