Leids Universitair Medisch Centrum

Centre for Bone Quality
Leiden University Medical Center

Denosumab: Summary of the LUMC clinical studies

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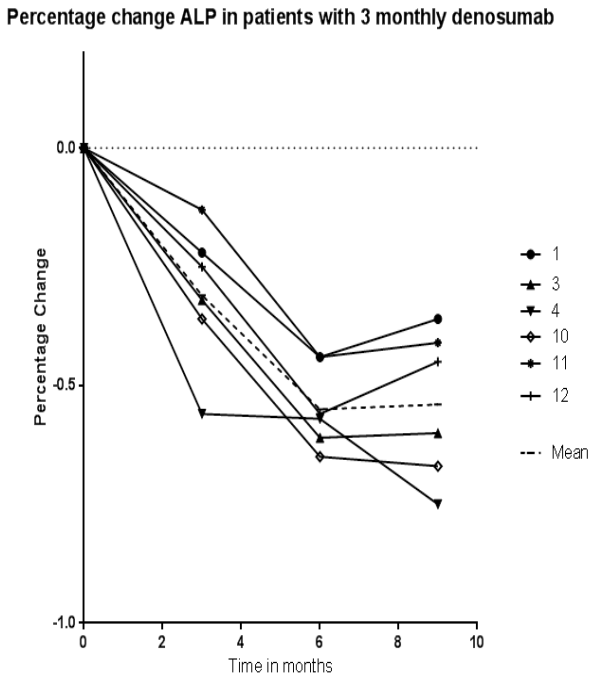
Denosumab in FD/MAS : a proof of concept

Centre for Bone Quality
Leiden University Medical Center

Dmab significantly decreased

- Bone turnover

1.A



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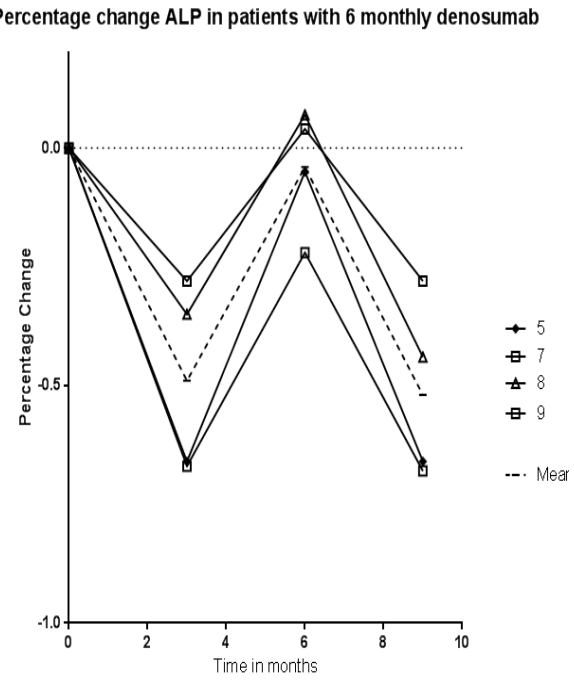

Majoor et al JCEM 2019

Denosumab in FD/MAS : a proof of concept

Dmab significantly decreased

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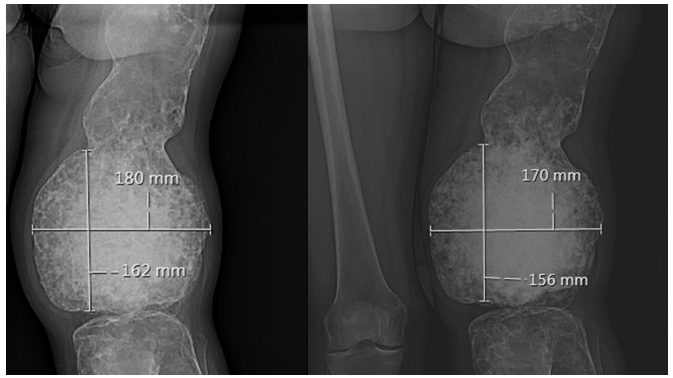
- Lesional activity on 18_NaF PET scans
- Lesion size
- Pain



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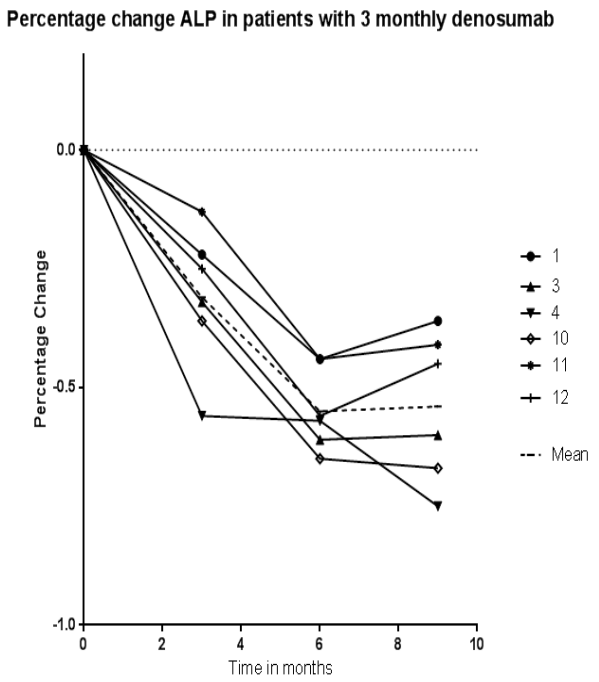

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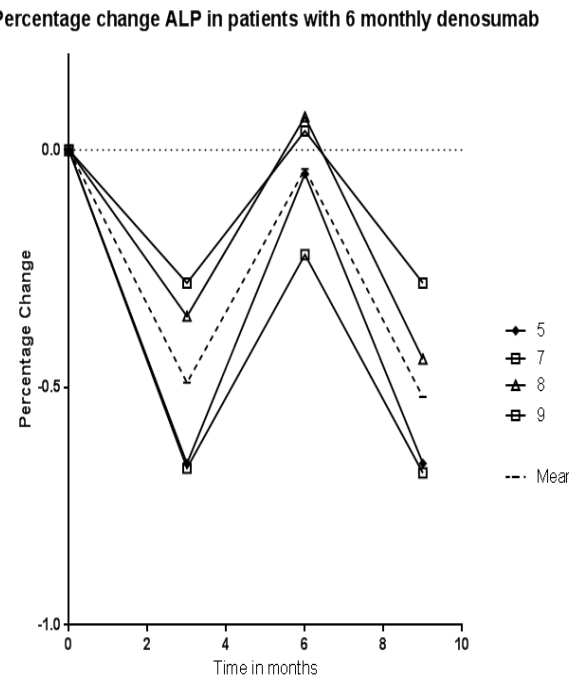

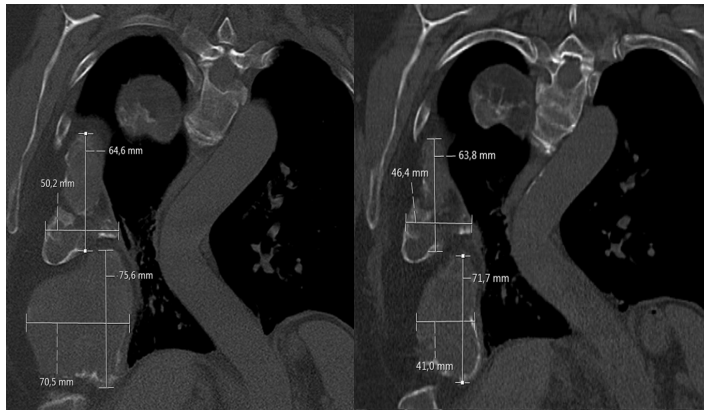

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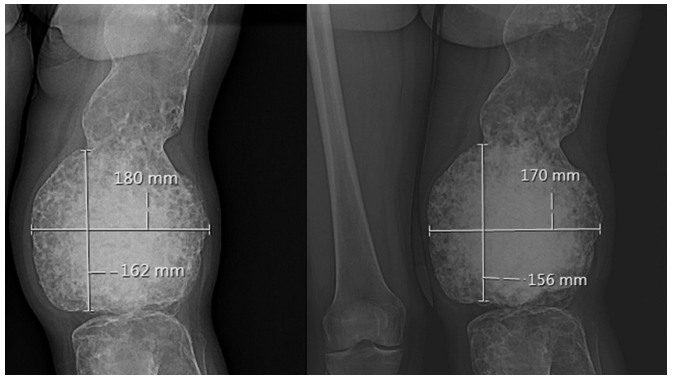

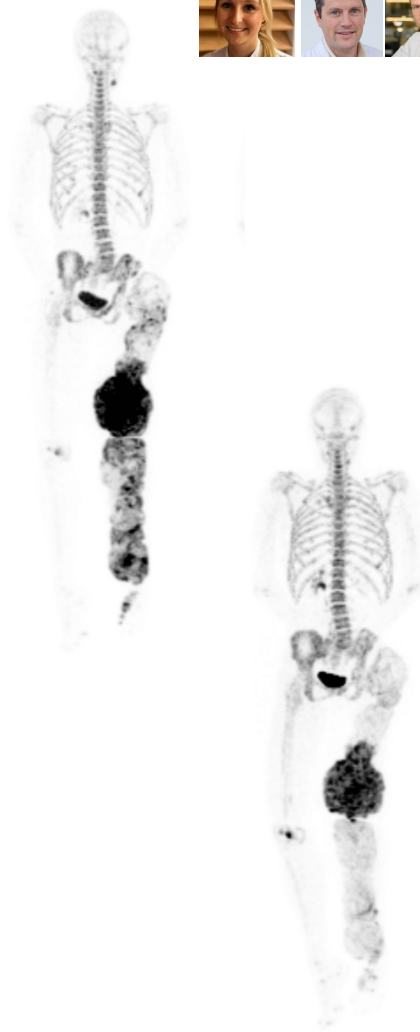

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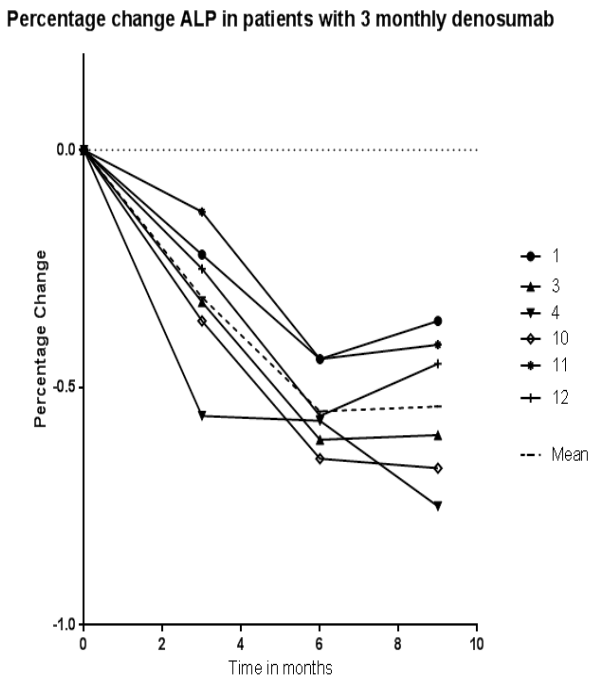

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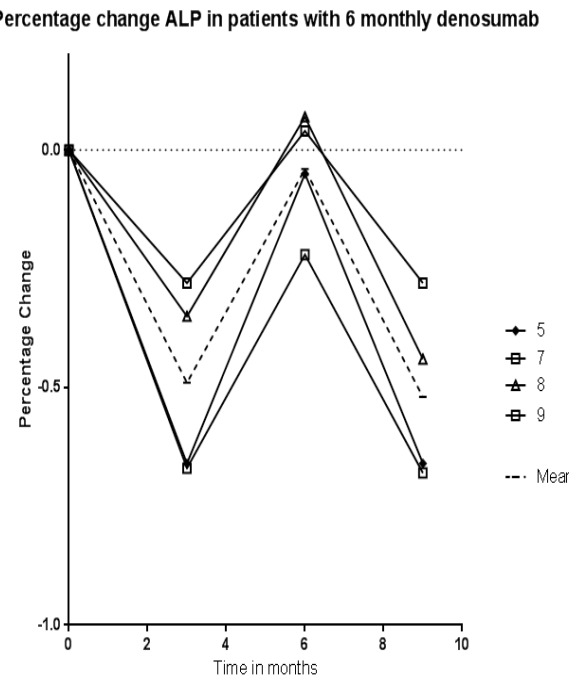

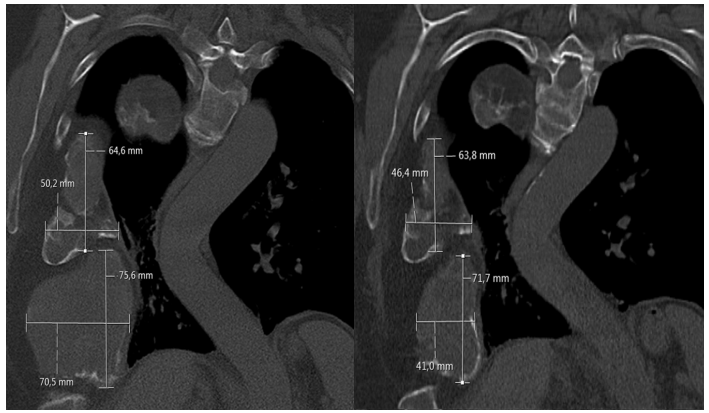

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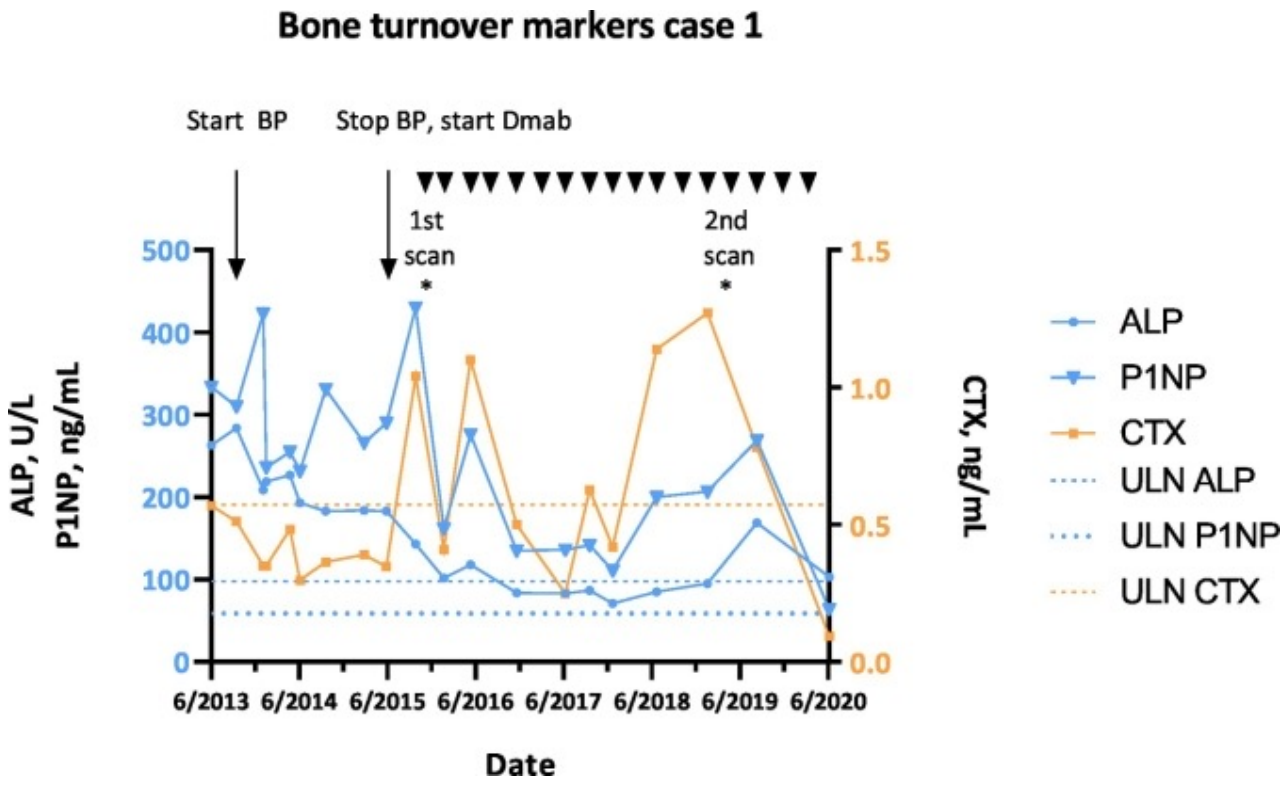
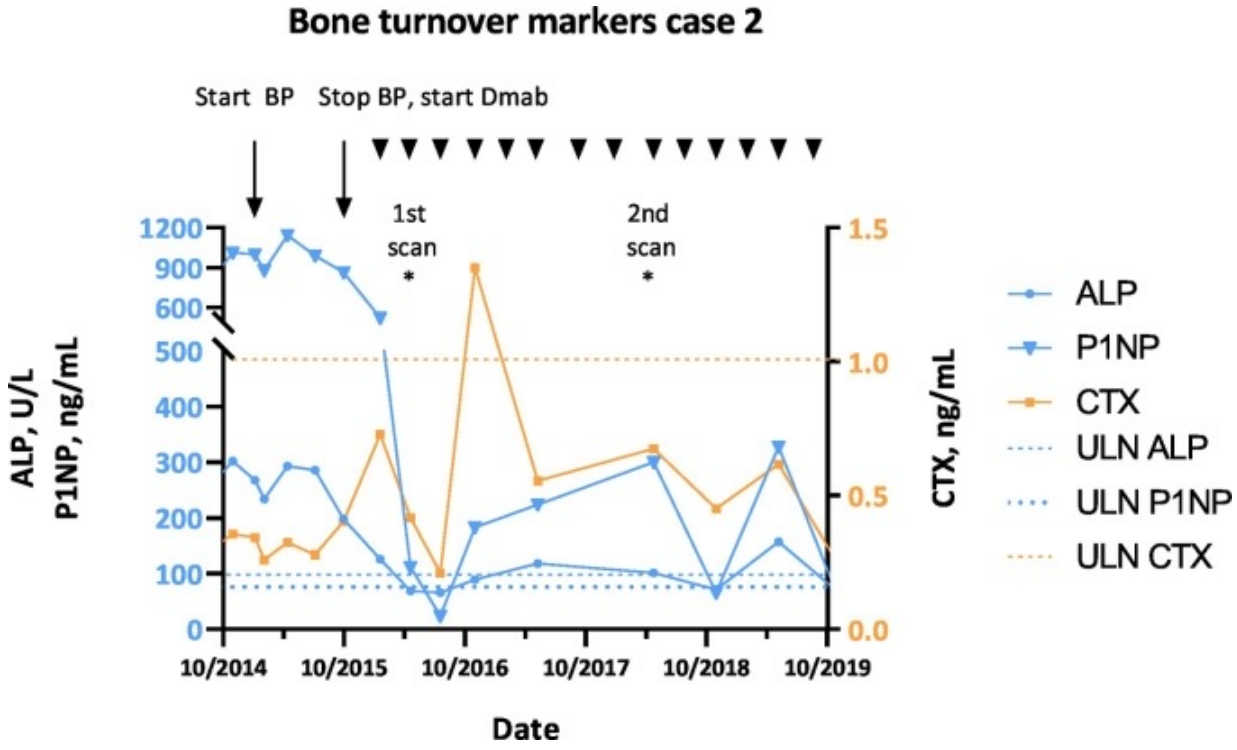
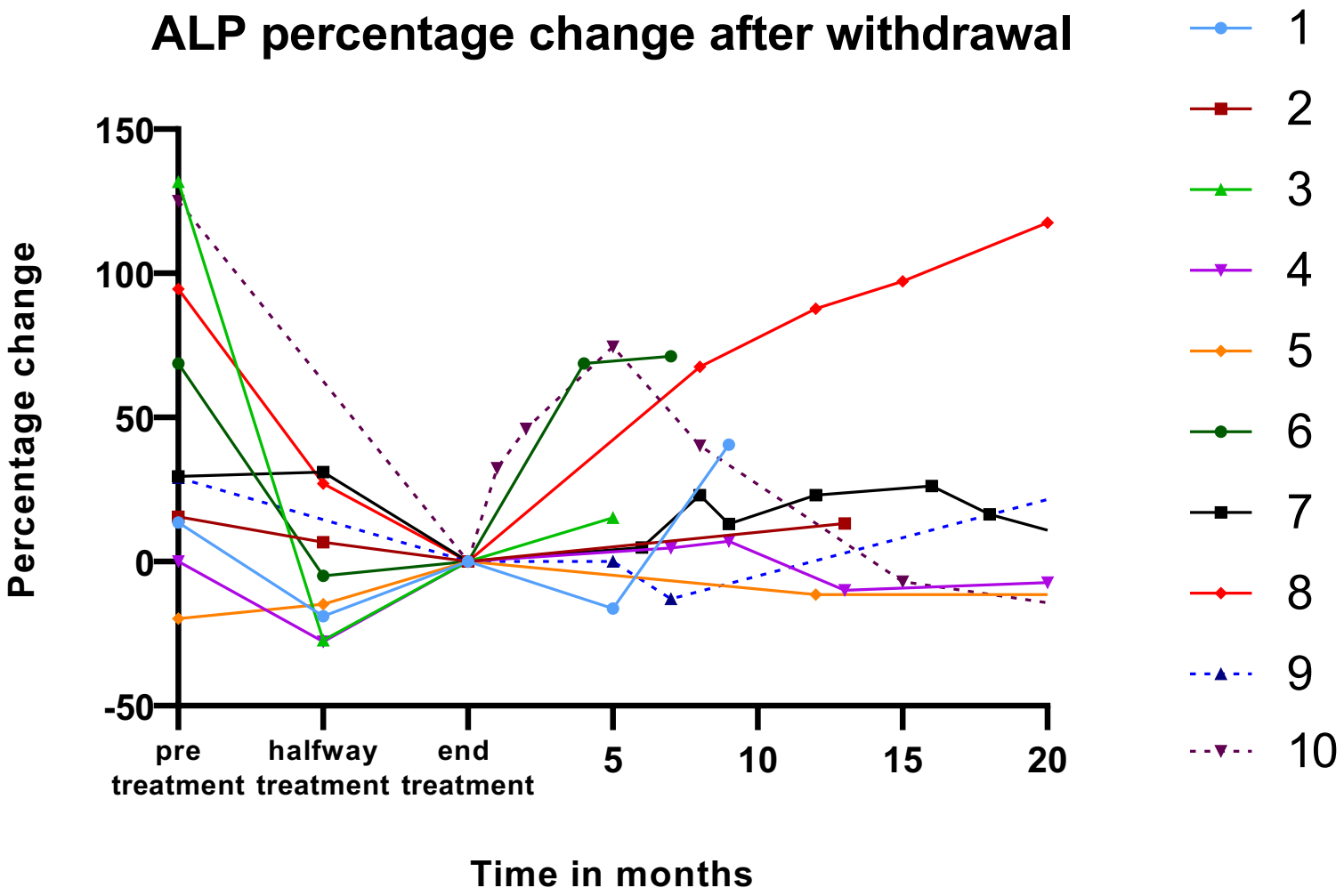
Denosumab in FD/MAS





Denosumab discontinuation in BP pretreated patients



Meier et al JBMR 2021

First author, year	Number of patients	Age patients (range/ age or mean)	Type of FD	Pain present	Previous BP treatment	Dmab (dose,interval)	Pain after dmab	Bone markers after dmab	Dmab effect on lesion on imaging
De Castro, 2023	8	19-54	7MAS, 1 CFD	Yes, median 6.4 (IQR 3.25)	-	120 mg every 4 weeks, with loading doses on weeks 2 and 3	**Decreased**	decreased	Decrease in lesion activity
Trojani, 2023	13	mean age 45 ± 14	4 MFD, 4 PFD, 5 MAS	Yes, severe (7.8/10 (±1.99)	Yes	Different schemes: 60 mg at 6 months, at 3 months 120 mg	**Decreased,** except one patient	-	Lesion decrease in one pt with cfd
Tucker-Bartley, 2023	2, one received dmab	24F;	MAS (CFD);	Yes	Yes	60 mg, 30 mg after one month, 30 mg after another month;	**Decreased**	-	-
Golden, 2022	2 ,one received dmab	21,F	Isolated cfd	Yes,severe (7-8/10)	No	120 mg at 6 months	**Unchanged**	-	-
Ikuta, 2021	1	27,F	MFD	Yes, severe (8/10)	No	120 mg days 1,8,15,29 and at 2 and 3 months	**Decreased**	TRACP-5b decreased	osteosclerotic changes
Meier 2021, JCEM	37	42 (19)	7MFD,21 PFD, 9 MAS	Yes 6.0 2.7 /10	Yes; 3 naive	60 or 120 mg of Dmab in intervals of 2, 3, 4, or 6 months	**Decreased**	ALP normalized(70 %); P1NP nor.alized (70%);	-

First author, year	Number of patients	Age patients (range/ age or mean)	Type of FD	Pain present	Bone markers before treatment	Previous BP treatment	Dmab (dose,interval)	Pain after dmab	Bone markers after dmab	Dmab effect on lesion on imaging
Raborn 2021	1	13 F	Isolated cfd	Yes	increased	Yes	1 mg/kg, monthly, 3.5 years	**Decreased,pain resolution** after 3.5 years	Normalized	no further FD expansion and increased lesion density
Van der Bruggen, 2021	8	-	PFD	Yes	ALP, P1NP increased	Yes	60 mg at 3 months; yes	**Decreased**	Decreased	Decreased disease activity
Gautam, 2020	1	45,F	PFD - reported Mas	Yes, severe	AF,P1NP, CTx increased	Yes	60 mg, 120 mg, 120 mg 6 months interval	**Decreased**	Normalized after 3 doses	-

First author, year	Number of patients	Age patients (range/ age or mean)	Type of FD	Pain present	Bone markers before treatment	Previous BP treatment	Dmab (dose,interval)	Pain after dmab	Bone markers after dmab	Dmab effect on lesion on imaging
Majoor, 2019	12	-	7PFD,4MAS, 1 severe CFD	Yes	AF, P1NP, CTx increased	Yes,	60 mg at 6 months and 60 mg every 3 months	**Decreased** in 10 of 12; **Resolution** in 6	Decreased, Normalized	-
Eller-Vainicher, 2016	1	20M	CFD (mfd-mandible)	Yes,severe 8-9/10	CTX upper normal, osteocalcin, b-ALP normal	yes	60 mg at 3 months	**Pain resolution**	Decrease	-
Benhamou, 2014	1	46M	PFD (rib,T1)	yes	CTX increased	Yes	60 mg at 6 months (two doses)	**Pain resolution** after 1 st dose	Decreased after 1 st	-
Ganda,	2	44F;48	CFD+PFD	Yes,	P1NP	Yes	1:60 mg,	**Decrease**	Normalized	-

First author, year	Number of patients	Age patients (range/ age or mean)	Type of FD	Pain present	Bone markers before treatment	Previous BP treatment	Dmab (dose,interval)	Pain after dmab	Bone markers after dmab	Dmab effect on lesion on imaging
Ganda, 2014	2	44F;48 M	CFD+PFD	Yes, severe	P1NP increased; b-ALP, P1NP increased	Yes	1:60 mg, second dose after 9 months, third after 6 months; 2:60 mg at 4 months	**Decreased**	Normalized	-
Boyce 2012	1	9, M	MAS	Yes, severe	P1NP, CTx increased	Yes	7 months, monthly 1 mg/ kg increased with 0.25 every 3 months	**Decreased**	Reduction f bone markers	

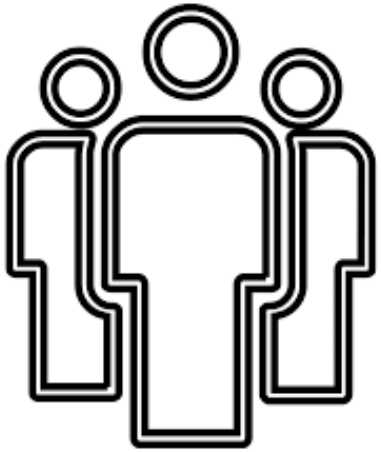
2 ongoing trials

Denosumab for pain in FD/MAS: Multicenter placebo controlled trial in **adults**

NCT05966064

Denosumab in FD/MAS: open label proof of concept trial on lesion development in children

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



- Adult patients with FDMAS
- Pain score from FD lesion for maximum or average pain on VAS ≥ 4

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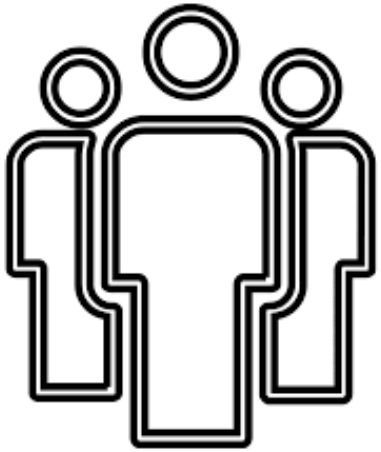

- Adult patients with FDMAS
- Pain score from FD lesion for maximum or average pain on VAS ≥ 4

- Denosumab 120 mg vs Placebo
- 3 monthly double blinded for 6 months
- Followed by open label for 6 months

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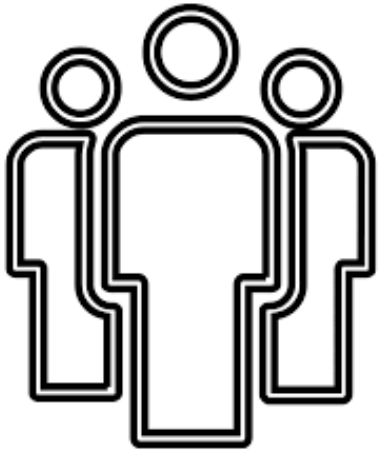

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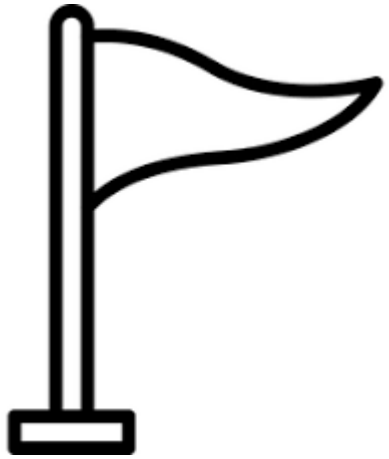


- **Difference in maximum pain score after 6 months**
- Dmab effect on Quality of life, physical activity
- Evaluation of possible neuropathic component of the reported pain
- Evaluation of analgesics use Evaluation of changes in mobility
- Dmab effect on FD lesion size and activity
- Dmab effect on bone density

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

Objective: 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.

Study population: Patients over 18 years old with an established diagnosis of FD/MAS on the basis of characteristic clinical and imaging features and persistent pain at the site of lesions with a maximum pain score of ≥4/10 as measured by the Visual Analogue Scale (VAS).

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

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 Na18F-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 severe 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

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

Main study parameter/endpoint

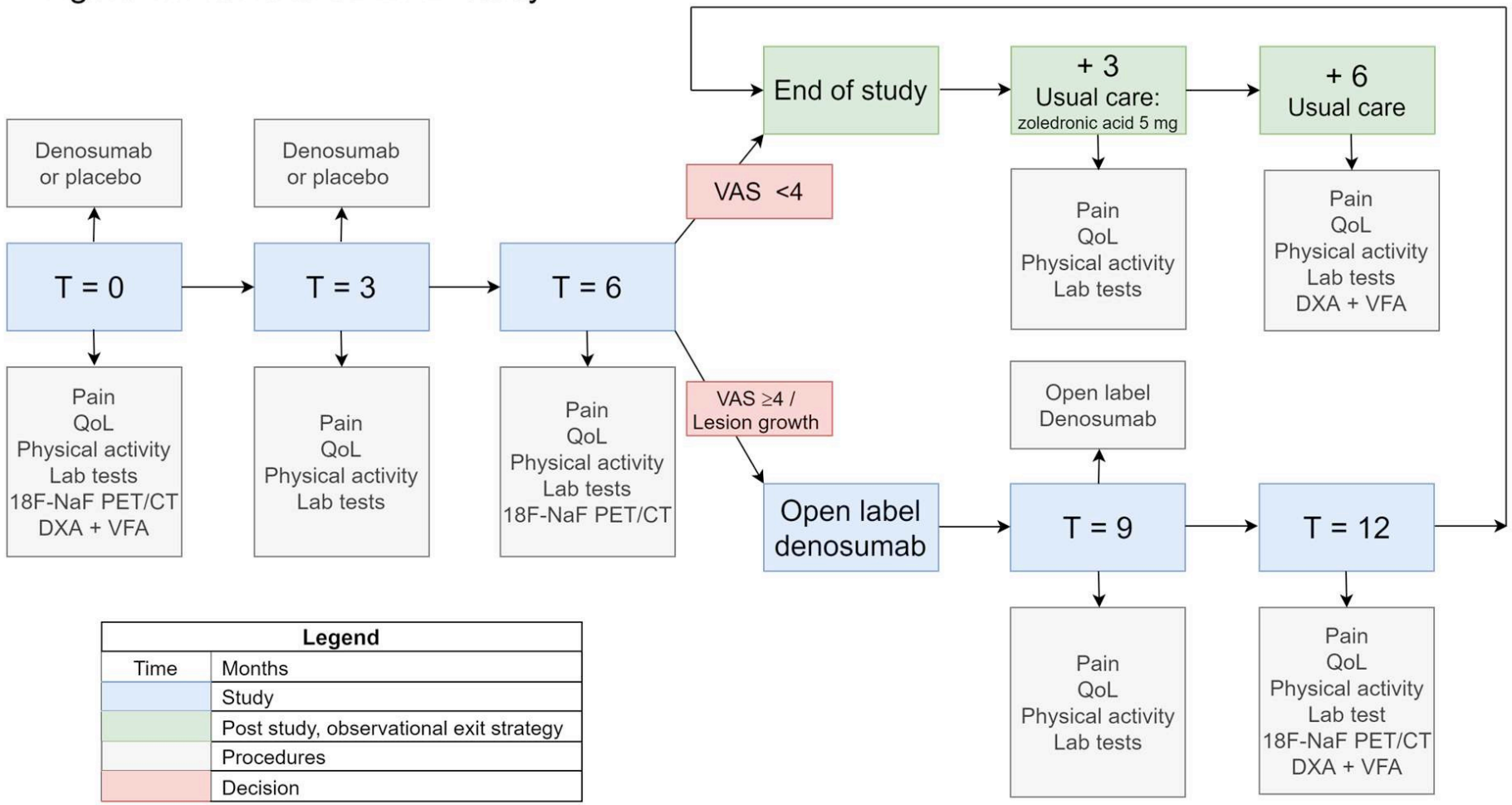
The effect of Dmab on pain, assessed by the difference in maximum pain score after 6 months (2 injections) by Brief Pain Inventory

Secondary study parameters/endpoints (if applicable)

- Dmab effect on **average pain scores** after 3, 6 months of treatment and in case of open label treatment after 9 and 12 months
- **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
- Dmab effect 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
- Dmab effect on **average weekly pain** assessed through a pain diary with VAS score
- Dmab eefct 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 at baseline, 3 months and 6 months and in case of open label treatment after 9 and 12 months
- 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

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

Figure 1. Flowchart DEFiD study



Legend	
Time	Months
	Study
	Post study, observational exit strategy
	Procedures
	Decision

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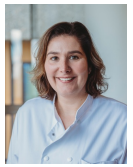

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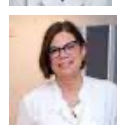

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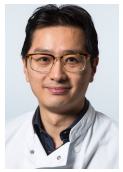

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EuRR-Bone study group
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