Lyos
Ostéoporose - Cancérologie osseuse - Lyon

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DFO
DYSPLASIE FIBREUSE DES OS

IL-6 inhibition in FD/MAS
Tocilizumab : Summary of the TOCIDYS Study and Follow-up

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Consortium meeting

OSCAR FILIÈRE SANTÉ MALADIES RARES

ERN BOND
EUROPEAN REFERENCE NETWORK
ON RARE BONE DISEASES

Disclosures

Research funding from Chugai Pharma

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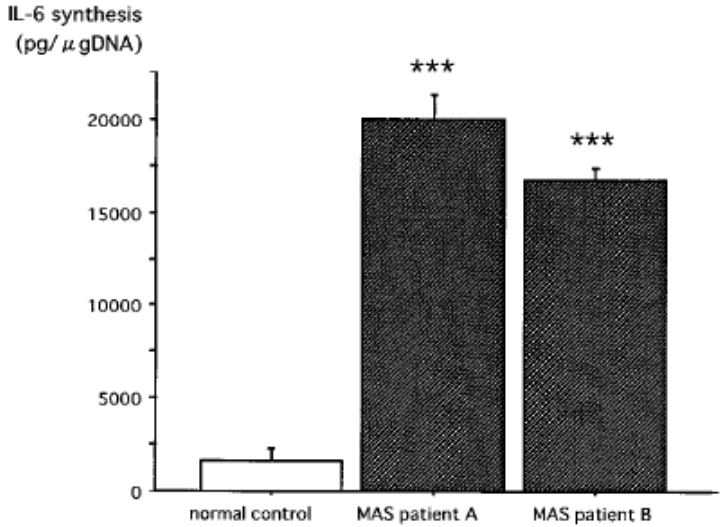
Increased IL-6 production by cells from FD/MAS bone tissue

IL-6 synthetis was increased in mutated cells



Yamamoto T, et al. JCI 1996

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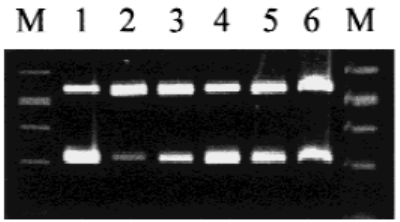
Glucocorticoids Decrease Interleukin-6 Levels and Induce Mineralization of Cultured Osteogenic Cells from Children with FD



Cell line	*Treatment*	*IL-6 levels (ng/ml)*
Normal	none	1467 ± 62
	dexamethasone	849 ± 68
	methylprednisolone	585 ± 23
Case 8	none	6038 ± 346
	dexamethasone	2670 ± 1225
	methylprednisolone	2472 ± 18
Case 10	none	1638 ± 64
	dexamethasone	804 ± 170
	methylprednisolone	704 ± 20

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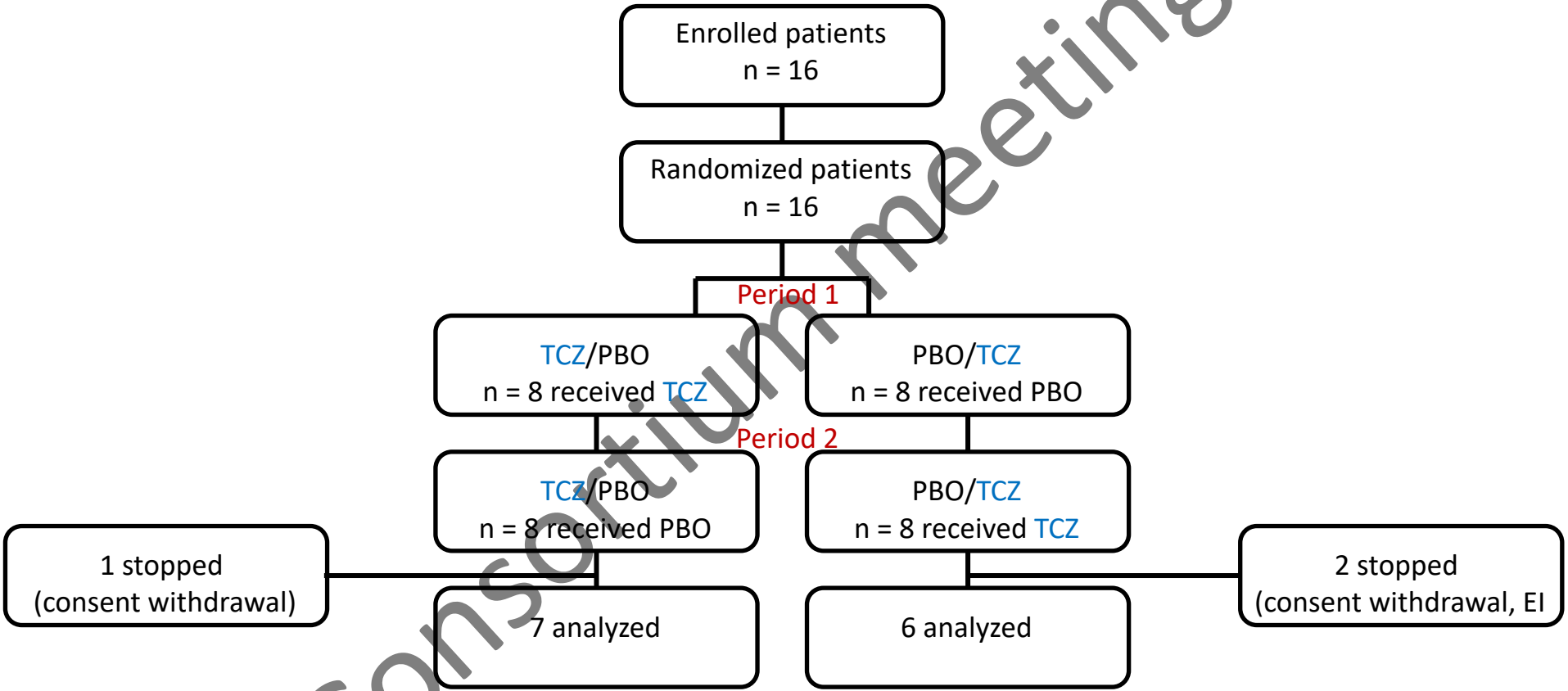
Stanton R et al. JBMR 1999

Inhibition of IL-6 by Tocilizumab: the TOCIDYS Trial



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Inhibition of IL-6 by Tocilizumab: the TOCIDYS Trial

Main Inclusion Criteria

Failure to respond to bisphosphonates

Bone pain (VAS) > 3 at the most painful bone site

At least 18 years of age

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Inhibition of IL-6 by Tocilizumab: the TOCIDYS Trial

Endpoints and Statistics

Primary endpoint:

Change in serum CTX after 6 months of treatment vs baseline

Secondary endpoints:

Change in bone pain

Change in P1NP, BAP, osteocalcin, ICTP

Quality of life (SF-36)

ANOVA, with sequence of treatment, period and treatment as factors and accounting for a potential carry-over effect

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Inhibition of IL-6 by Tocilizumab: the TOCIDYS Trial

Characteristics at Inclusion

	TCZ/PBO (N=8)	PBO/TCZ (N=8)
Mean age, years (SD)	50.7 (0.9)	50.3 (1.4)
Sex		
Women	6 (75.0%)	8 (100.0%)
Men	2 (25.0%)	0 (0.0%)
Weight, kg (mean, SD)	64.3 (16.5)	59.8 (13.4)
Height, cm (mean, SD)	165.4 (11.4)	157.4 (7.5)
BMI, kg/m^2	23.6 (5.1)	24.2 (5.6)
Symptoms onset (years)	16.0 (10.0)	31.0 (16.3)
Precocious puberty	2 (28.6%)	3 (37.5%)
Pain intensity	5.4 (1.6)	6.1 (1.2)
CTX (pg/ml)	581.9 (279.9)	642.2 (212.2)

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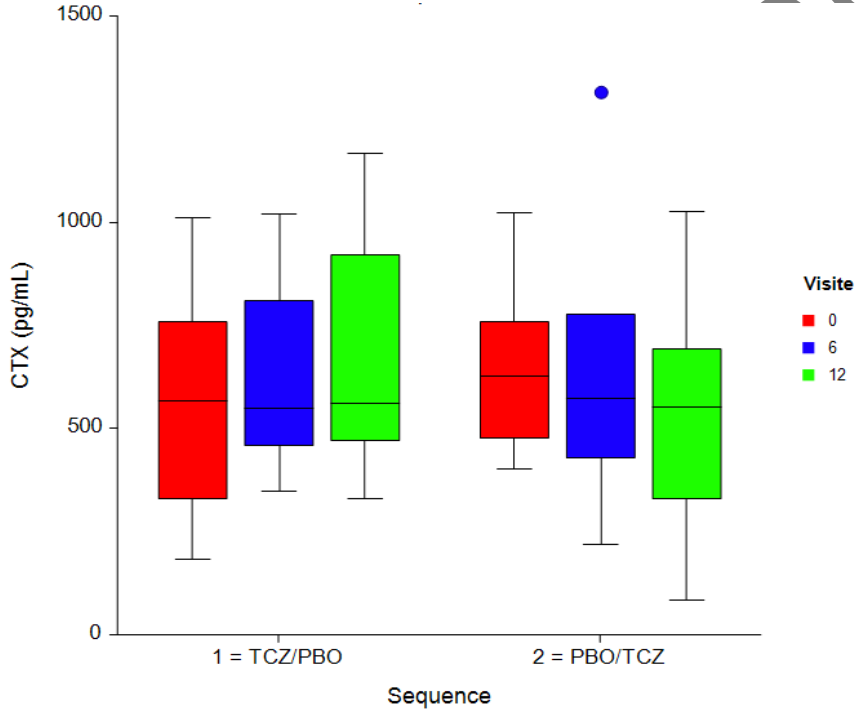
Inhibition of IL-6 by Tocilizumab: the TOCIDYS Trial

Change in Serum CTX, Efficacy Population



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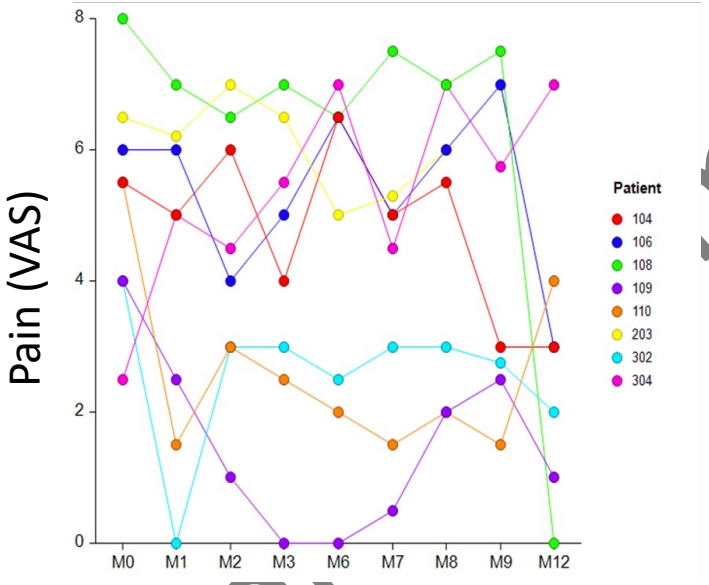
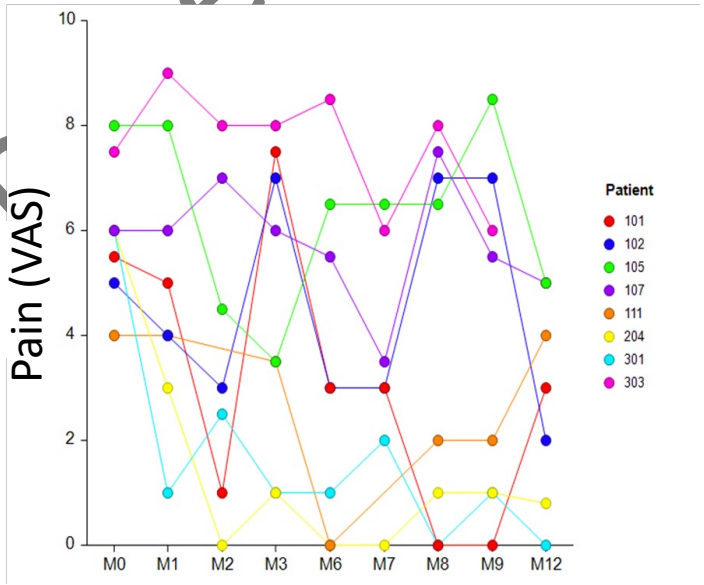
Change in Bone Pain, Individual Trajectories

TCZ/PBO Sequence



PBP/TCZ Sequence



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Inhibition of IL-6 by Tocilizumab: the TOCIDYS Trial

Summary

Tocilizumab does not decrease bone turnover in FD when administered in patients who fail to respond to bisphosphonates.

Tocilizumab does not reduce bone pain in most patients, but a substantial effect in a subset cannot be ruled out in this trial designed and powered for markers but not for pain.

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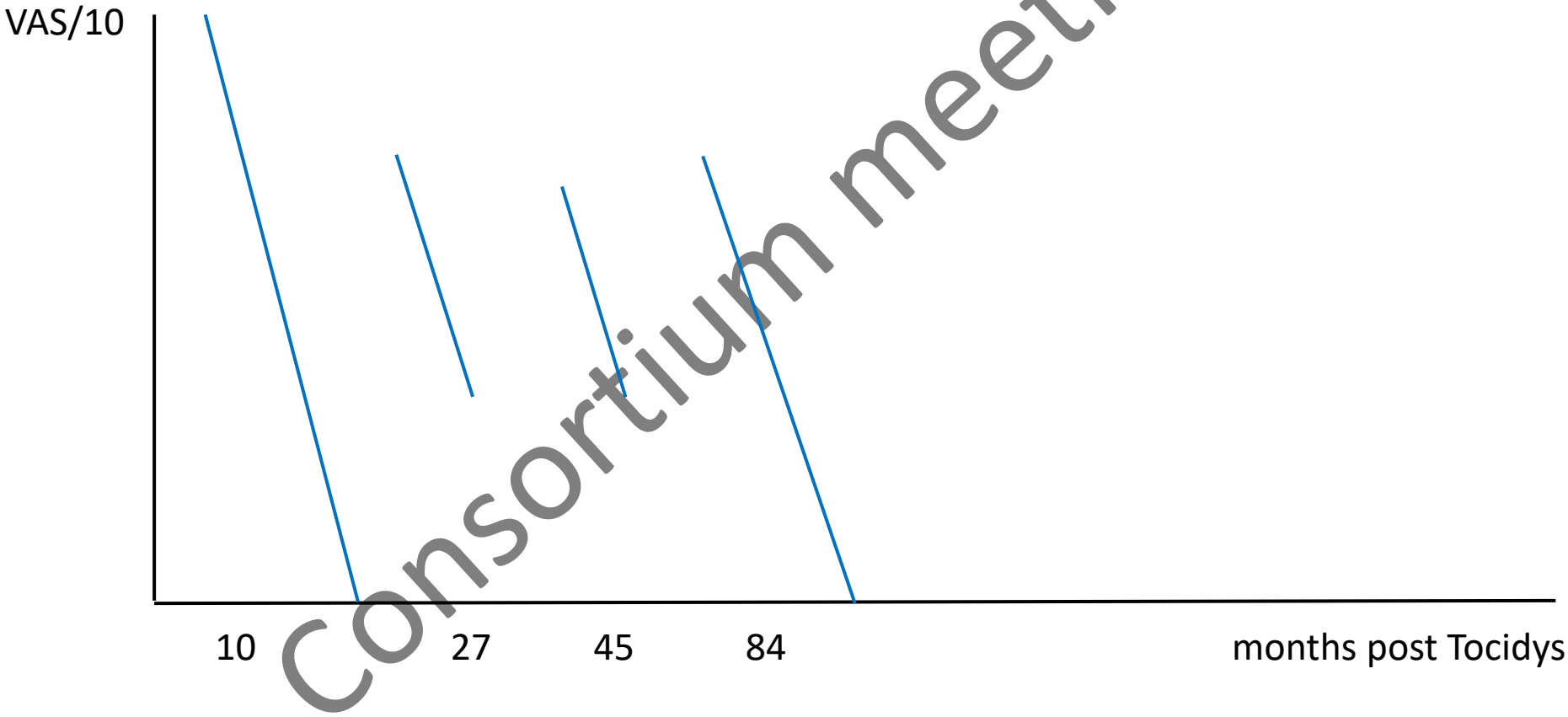
Follow-up of Patients who responded to TCZ

Patient 1



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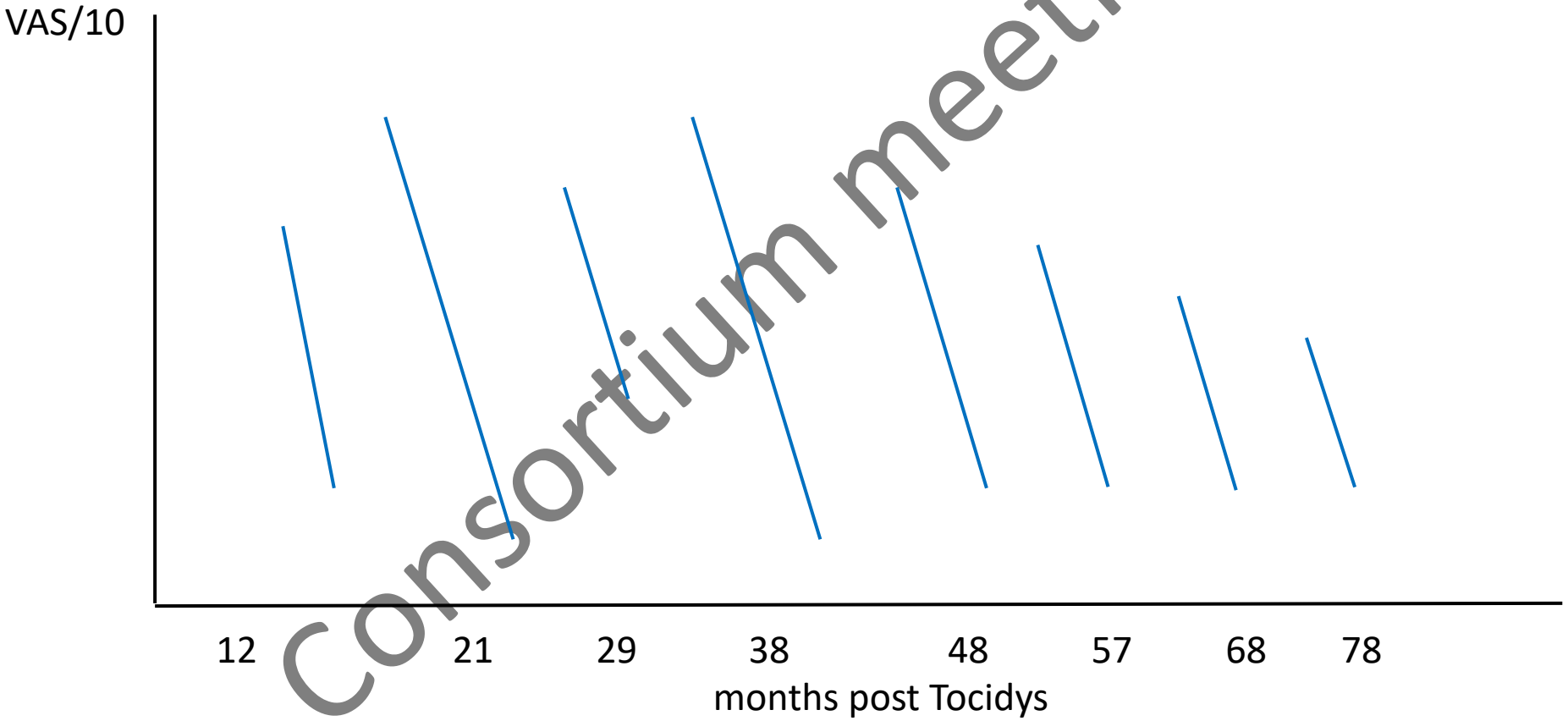
Follow-up of Patients who responded to TCZ

Patient 2



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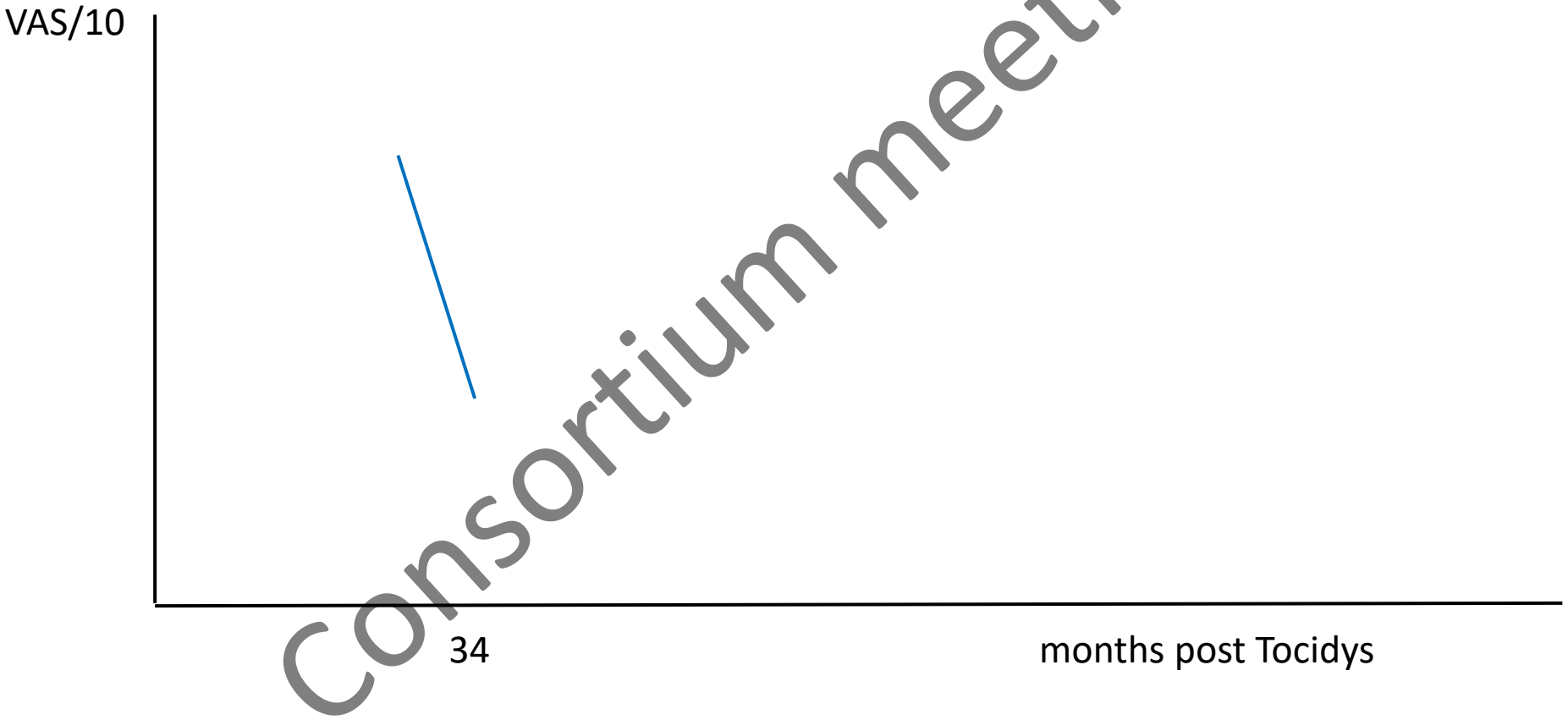
Follow-up of Patients who responded to TCZ

Patient 3



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Conclusion

Tocilizumab does not influence bone markers

Observations from the randomized trial and from the follow-up of 3 patients post trial are consistent with a sizeable reduction in bone pain in a subset of patients.

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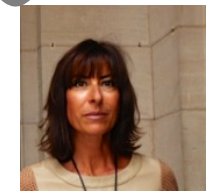
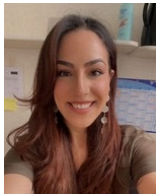
Aknowledgements

INSERM UMR 1033, FD National Reference Center





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Funding from French Ministry of Health and Chugai Pharma

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DYSPLASIE FIBREUSE DES OS

A DOUBLE-BLIND RANDOMIZED PLACEBO-CONTROLLED TRIAL TESTING RISEDRONATE TO TREAT FIBROUS DYSPLASIA OF BONE - *THE PROFIDYS TRIAL*

Roland Chapurlat, Neveen Hamdy, Jean-Pierre Devogelaer, Deborah Gensburger, Cedric Trolliet, Socrates Papapoulos, Laredo JD, Philippe Orcel

Silver Spring MD, September 10th 2023

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Osteoporosis - Bone Metastasis - Lyon

Background

Bisphosphonates have been widely used in the treatment of fibrous dysplasia of bone for > 20 years

Positive results were obtained from uncontrolled studies of IV bisphosphonates

Their use has been advocated to reduce bone pain, improve bone strength and imaging aspects

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Background

In the 1990s, the bisphosphonates doses were comparable to those used in the treatment of Paget's disease of bone

A randomized placebo-controlled trial comparing alendronate to placebo has not shown a significant effect on bone pain and imaging, but a reduction in bone turnover

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Background

We have tested the value of another oral bisphosphonate – risedronate – in the treatment of fibrous dysplasia of bone

We wanted to answer two main research questions:

- *Does risedronate reduce the level of bone pain?*
- *Does risedronate improve the radiological aspect of bone lesions?*

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Methods

Eligible Patient
No contra-indication,
Bisphosphonate naïve
Signed informed consent

BONE PAIN	***ASYMPTOMATIC***
VAS ≥ 3	***Osteolytic lesion(s)***
Study I	Study II
Randomization Risedronate versus placebo 1 year	***Randomization*** Risedronate versus placebo 3 years

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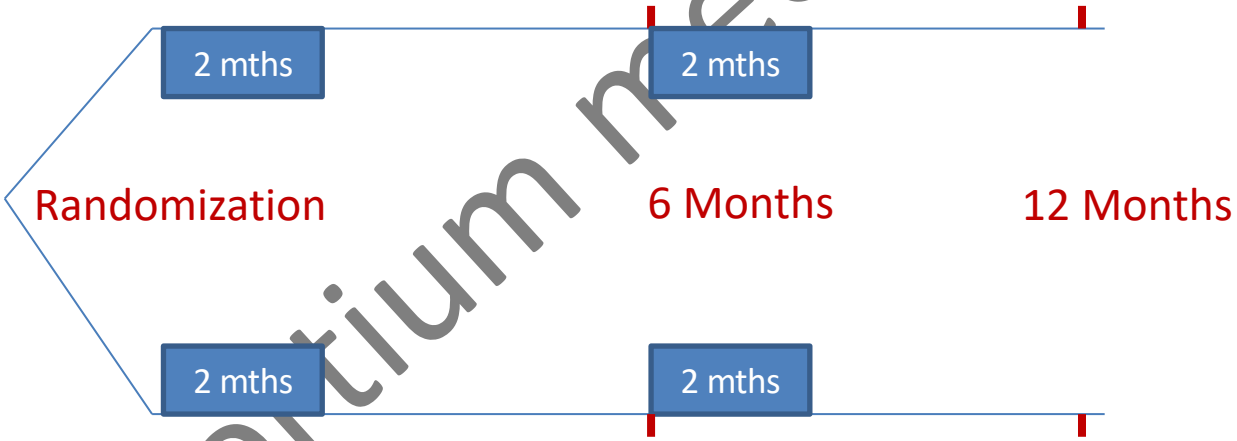
Methods

Two repeated cycles of therapy per year

Ca 1000 mg + Vitamin D3 800 IU + placebo



Ca 1000 mg + Vitamin D3 800 IU + risedronate 30 mg

nb: calcitriol + phosphate in those with renal phosphate wasting

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Methods

Inclusion/non inclusion criteria

INCLUSION

At least one measurable osteolytic lesion (CT)

NON INCLUSION

other metabolic bone diseases, ongoing malignancy, history of esophagitis, CKD with CG < 25 ml/min, severe hepatic diseases, history of uveitis, untreated rickets or osteomalacia, allergy to BPs, prior use of BP or fluoride, pregnancy and breastfeeding

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Methods

Visits

At inclusion

One month (motivation)

Six months and every 6 months thereafter

Phone calls /3 months

CT at beseline and 3 years or end of study

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Methods

Endpoints

PRIMARY

Radiological improvement (SQ)

SECONDARY

Change in quality of life (SF-36)

Change in BTM (CTX, BAP)

BMD changes (only affected hip)

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Methods

Principles of the Radiological Evaluation : quantification of change

0 no change

1 uncertain change

2 small but certain

3 certain and important

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Methods

Principles of the Radiological Evaluation : type of change

Diffuse

Wall

Peripheral

Recorticalization

Irregular

Other

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Methods

Randomization

Centralized

Blocks of four

Stratification by clinical centers

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Methods

Statistics

The sample size was calculated on the premise that RIS would allow for improvement in 50% of patients on risedronate, with an improvement in 10% of patients in the placebo group, with $\alpha = 0.05$, $\beta = 0.90$, with drop-out rate = 8% (Lachin): 59 patients

Fisher exact test for the primary endpoint of proportions of patients with improvement in radiological aspect

Per-protocol analysis

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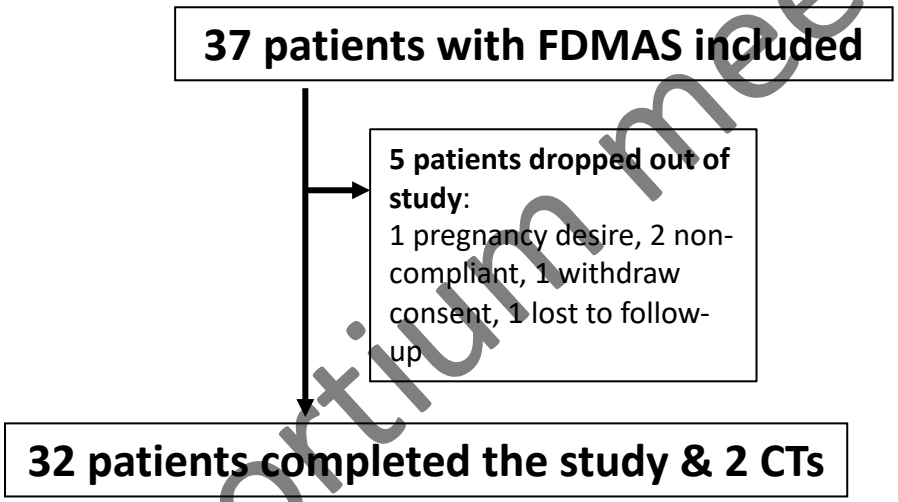
Flow-chart of the study



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Results: Baseline Characteristics

Characteristics	All patients (N= 32)	Placebo (N=16)	Treated (N=16)
Sex: women. % (n. N)	56.3 (18/32)	50 (8/16)	62.5 (10/16)
Age (years).	47.2 ± 13.7	47.0 ± 13.6	47.3 ± 13.9
BMI (kg/m^2).	25.37±4.74	26.74±5.37	24±3.7
Age 1st symptoms	34.07±16.4	35.27±15.31	33.03±17.76
Deformities. % (n. N)	20 (6/30)	33.3 (5/15)	6.7 (1/15)
Fractures. % (n. N)	20 (6/30)	13.3 (2/15)	26.7 (4/15)
Café-au-lait spots. % (n. N)	16.7 (5/30)	13.3 (2/15)	20 (3/15)
Endocrine complications % (n. N)			
* precocious puberty	10 (3/30)	6.7 (1/15)	13.3 (2/15)
* thyroid disorders	10 (3/30)	0	20 (3/15)
* other endoc. symptoms	17.2 (5/29)	6.7 (1/15)	28.6 (4/14)
Other symptoms	53.1 (17/28)	42.9 (6/14)	78.6 (11/14)

Results: Change in CT aspect

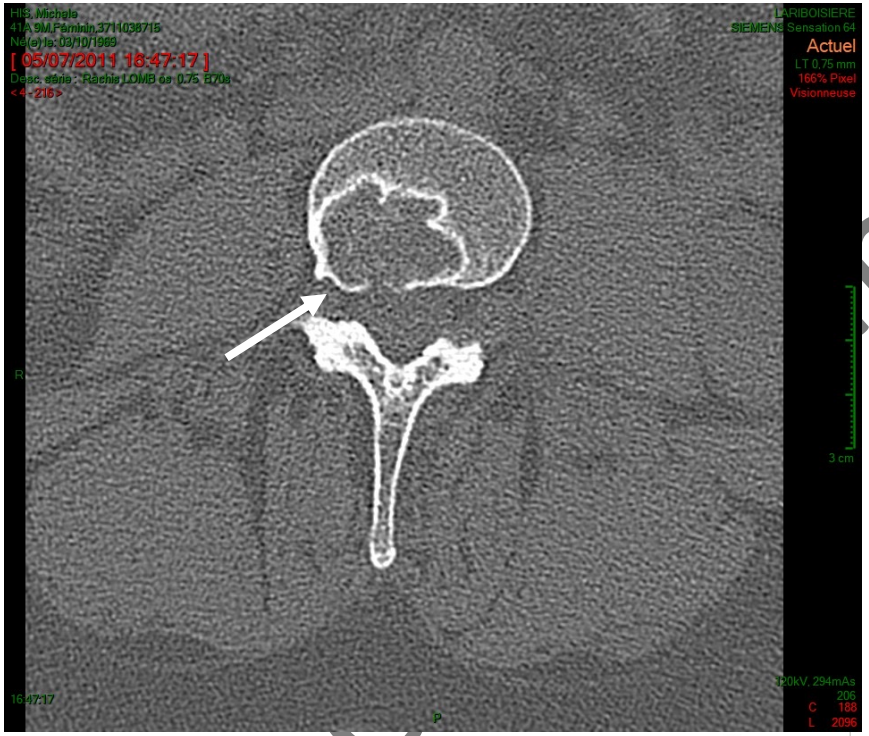
	Positive change	No change	Negative change
Placebo	2	14	0
Risedronate	2	13	1

Cons ting

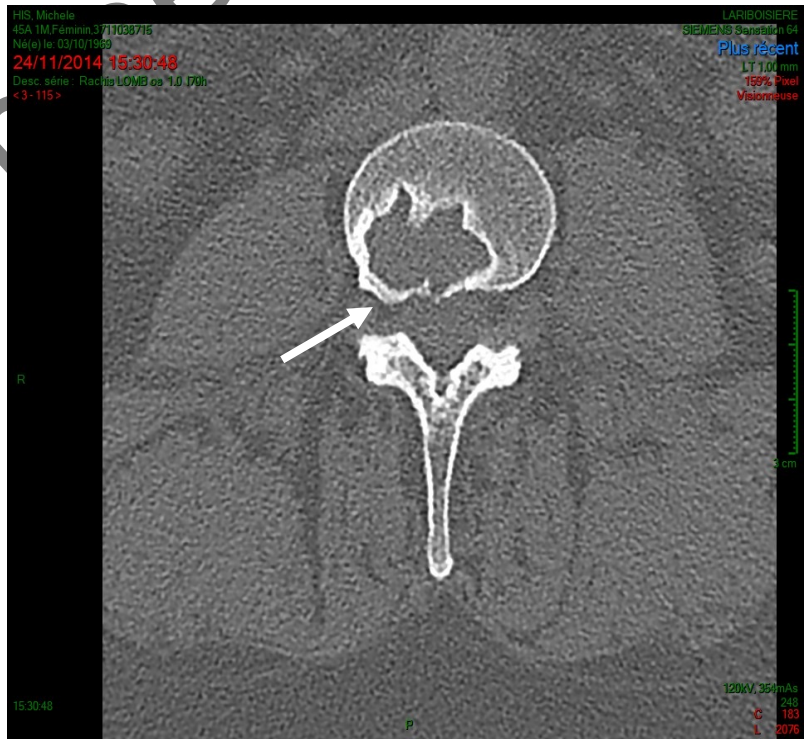
Results

Example, on risedronate

Before



After

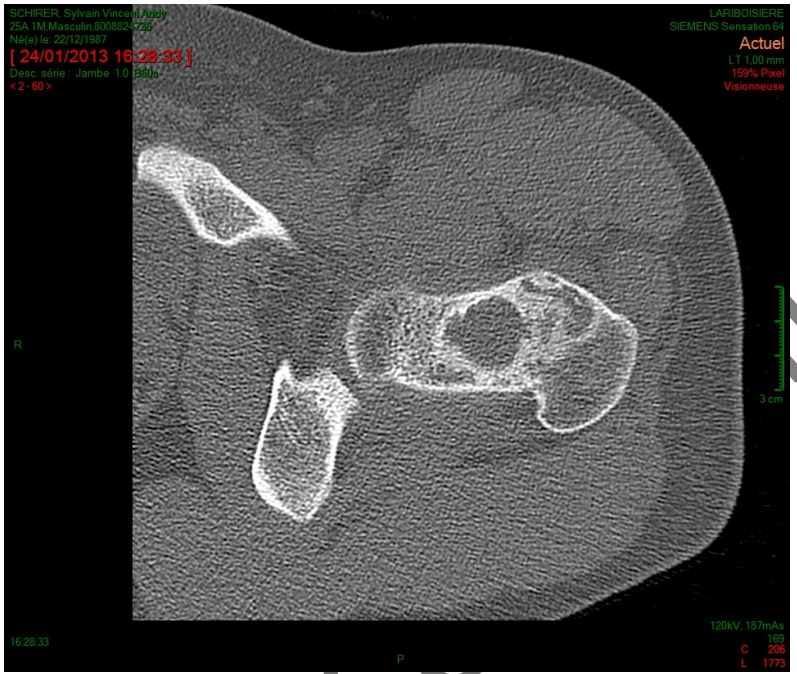


Current meeting

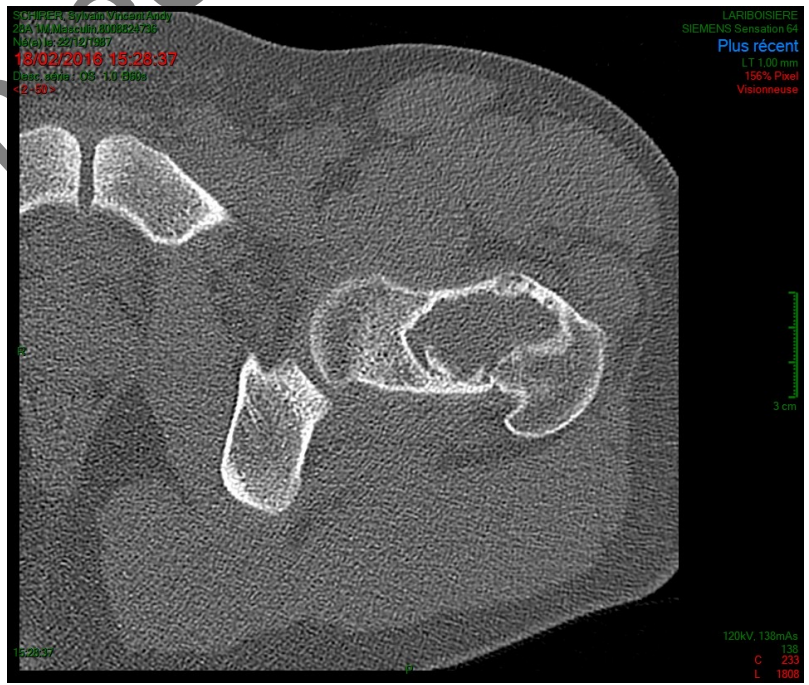
Results

Example, on risedronate

Before



After



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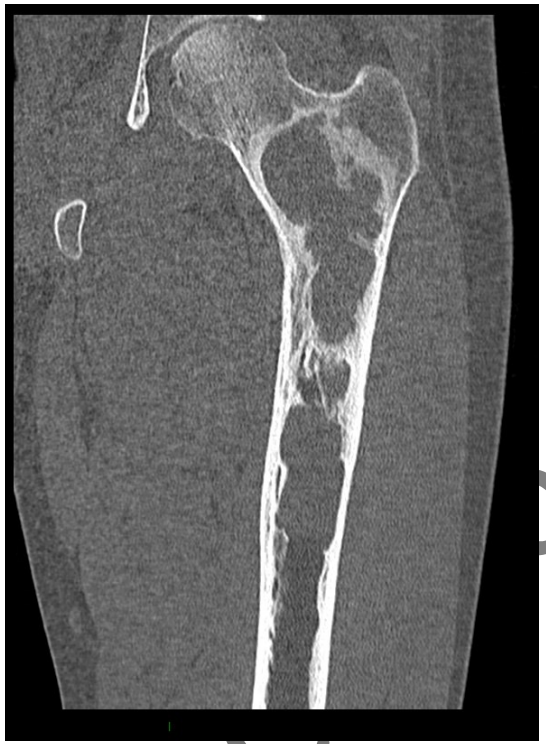
Results

Example, on risedronate

Before



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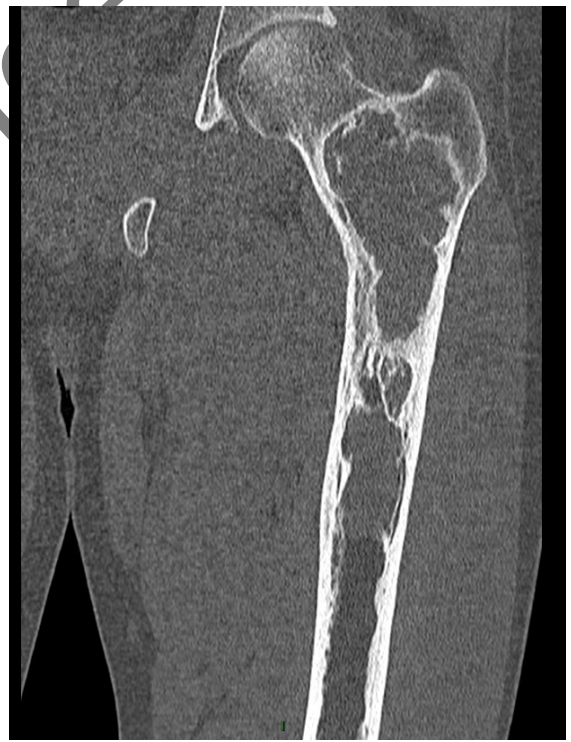

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Conclusion

The primary endpoint of more frequent CT improvement on risedronate compared with placebo was not met.

The study is underpowered, but a substantial difference can be ruled out

We show anecdotal evidence that:

- Impairment on risedronate is possible
- Natural improvement is possible

Using CT as an outcome for trials is feasible

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Aknowledgements

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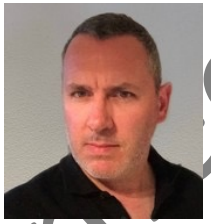

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Funding:

National agencies for the 3 countries

Procter and Gamble, Warner Chilcott