Welcome!

FLS Bone Health ECHO® TeleECHO Clinic

We will be recording this TeleECHO Clinic for educational and quality improvement purposes.

By participating in this clinic you are consenting to be recorded.

If you do not wish to be recorded, please email andrea.medeiros@nof.org at least one week prior to the TeleECHO Clinic you wish to attend.

Please type in your name, location, and email address in the chat.

Clinic will start in less than 15 minutes

Some helpful tips:

Please mute your microphone when not speaking

Position webcam effectively

Communicate clearly during clinic:

- Speak clearly
- Use chat function

Project ECHO's goal is to protect patient privacy

To help Project ECHO accomplish that goal, please only display or say information that doesn't identify a patient or that cannot be linked to a patient.

References:

For a complete list of protected information under HIPAA, please visit www.hipaa.com

Common HIPAA Identifier Slip-Ups and Easy Ways to Protect Patient Privacy

1st – **Names:** Please do not refer to a patient's *first/middle/last name* or use any *initials*, etc. Instead please use the *ECHO ID*.

2nd – **Locations:** Please do not identify a patient's *county, city or town*. Instead please use only the patient's *state* if you must or the *ECHO ID*.

3rd – **Dates:** Please do not use any dates (like *birthdates*, etc.) that are linked to a patient. Instead please use only the patient's *age* (unless > 89)

4th – **Employment:** Please do not identify a patient's *employer*, work *location* or *occupation*. Instead please use the *ECHO ID*.

5th – **Other Common Identifiers:** Do not identify patient's *family* members, *friends, co-workers, numbers, e-mails*, etc.

NOF Staff Disclosures

Andrea P. Medeiros, Director, Programs, Policy & Membership:
Nothing to Disclose

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Nothing to Disclose

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Mechanism of Action of Osteoanabolic Agents at the Tissue Level

David W. Dempster, PhD, FRMS
Columbia University, New York

Disclosures

- **Eli Lilly & Co**. : Research grants, Consulting and speaker fees

- **Amgen, Inc:** Research grants, Consulting and speaker fees

- **Radius Health:** Research grants, Consulting and speaker fees

Learning Objectives

1. Understand the differences in the mechanism of action of anabolic versus antiresorptive agents.

2. Differentiate the mechanism of action of PTH1-receptor agonists and sclerostin antibodies.

3. Understand the difference between remodeling- and modeling-based bone formation.

Anabolic vs Antiresorptive

Anabolic and Antiresorptive drugs both increase BMD and lower fracture risk, *but they do so by fundamentally different mechanisms*

Anabolic Drugs…	**Antiresorptive Drugs…**
Improve bone microarchitecture	Maintain bone microarchitecture
Increase bone formation; increase or reduce bone resorption	Reduce bone resorption and formation
Reduce mineralization density by shortening secondary mineralization	Increase mineralization density by prolonging secondary mineralization
Increase stress risers (resorption cavities)	Reduce stress risers (resorption cavities)
Stimulate modeling-based bone formation (MBBF)	Preserve modeling-based bone formation (MBBF)
Maintain osteocyte viability and add new osteocytes and/or replace old osteocytes	Maintain osteocyte viability

ORIGINAL ARTICLE

JBMR®

Remodeling- and Modeling-Based Bone Formation With Teriparatide Versus Denosumab: A Longitudinal Analysis From Baseline to 3 Months in the AVA Study

David W Dempster,[1,2] Hua Zhou,[1] Robert R Recker,[3] Jacques P Brown,[4] Christopher P Recknor,[5] E Michael Lewiecki,[6] Paul D Miller,[7] Sudhaker D Rao,[8] David L Kendler,[9] Robert Lindsay,[1,2] John H Krege,[10] Jahangir Alam,[10] Kathleen A Taylor,[11] Thomas E Melby,[12] and Valerie A Ruff[11]

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[6]New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM, USA
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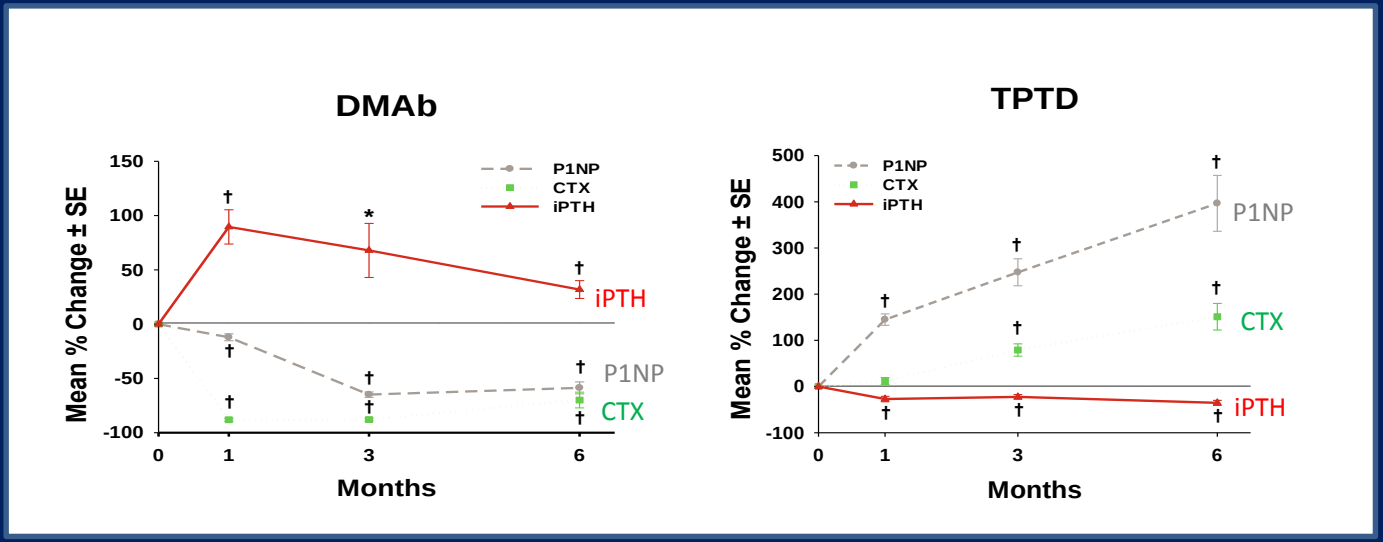
[8]Bone & Mineral Research Laboratory, Henry Ford Hospital, Detroit, MI, USA
[9]Department of Medicine (Endocrinology), University of British Columbia, Vancouver, Canada

Dempster et al. *J Clin Endocrinol Metab*. 2016;101(4):1353-1363

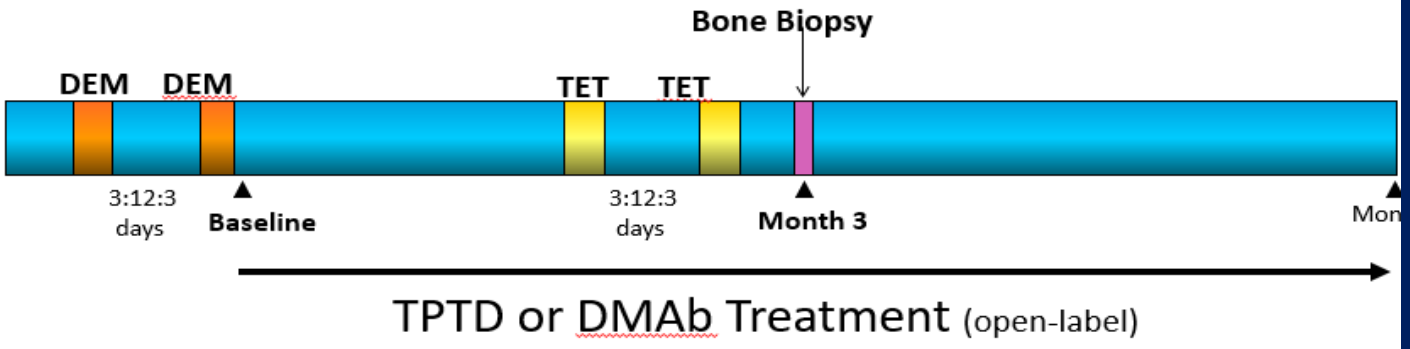
Intact PTH and Bone Turnover Markers



Dempster et al. *J Clin Endocrinol Metab*. 2016;101(4):1353-1363

AVA – Quadruple Labeling

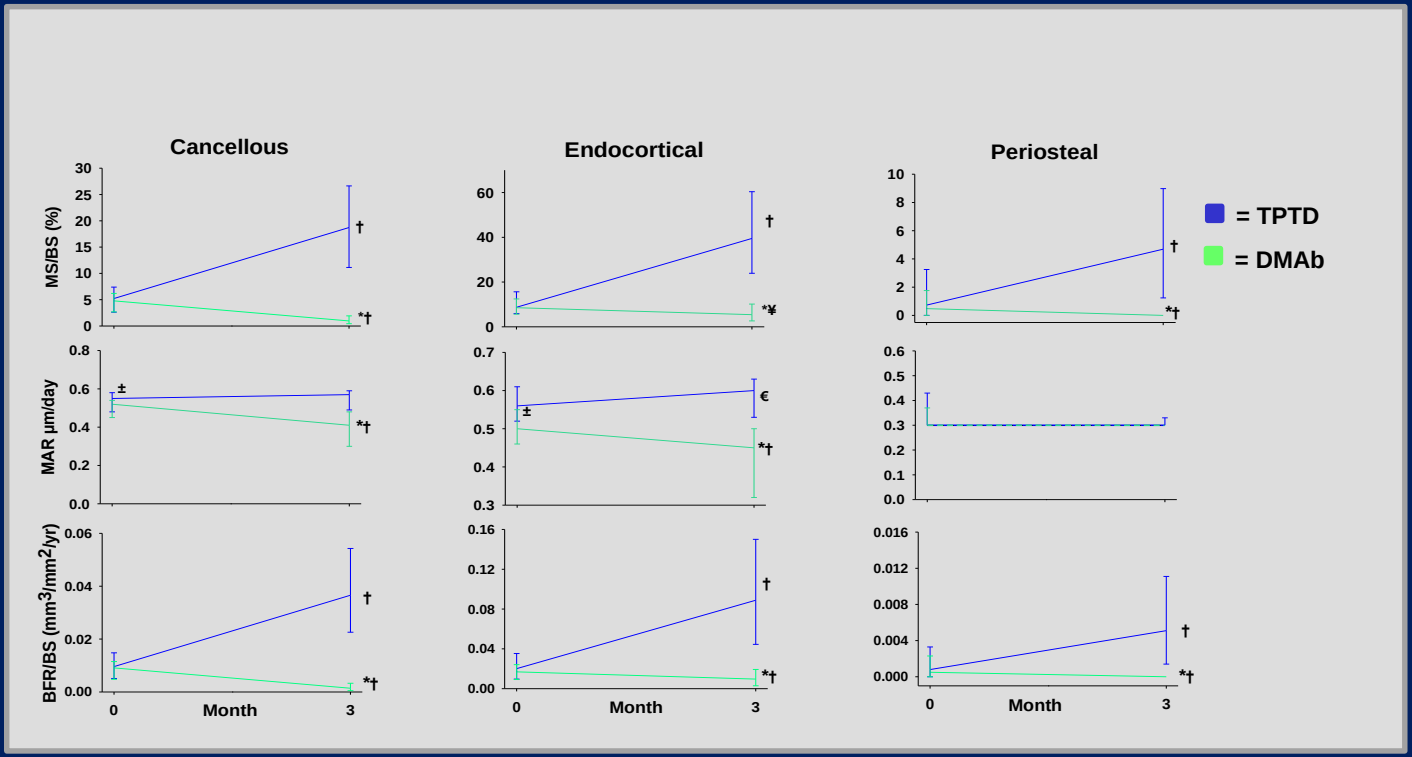
66 biopsies were collected; TPTD=31, DMAb=35



Abbreviations: DEM = demeclocycline; TET = tetracycline

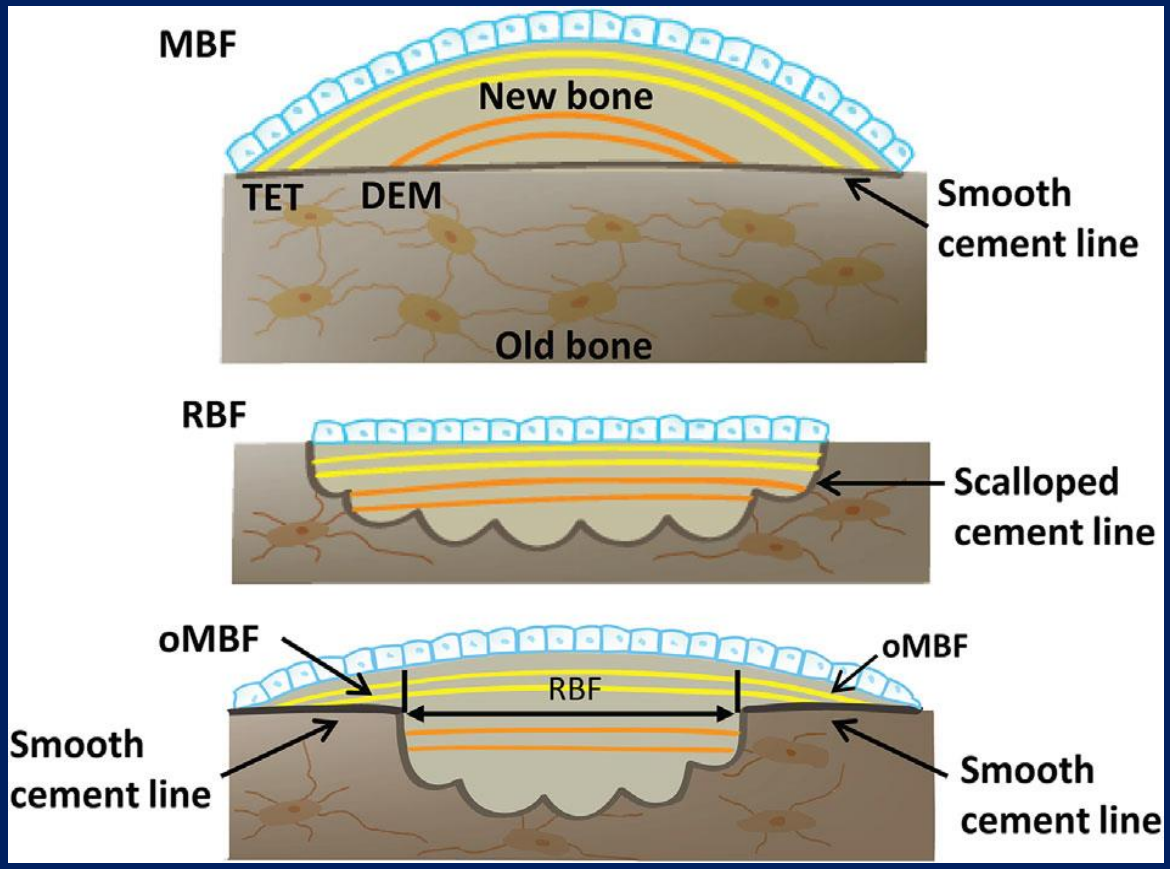
Dempster et al. *J Clin Endocrinol Metab*. 2016;101(4):1353-1363

AVA – Histomorphometry



Dempster et al. *J Clin Endocrinol Metab*. 2016;101(4):1353-1363

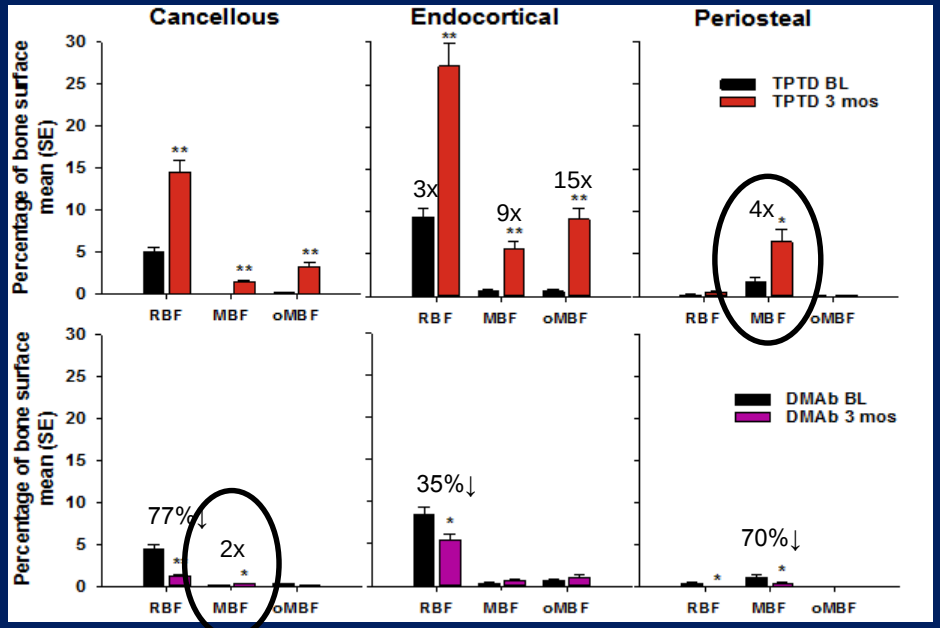
Cartoon Illustrating Three Types of Bone Formation



MBF: Modeling-based formation
RBF: Remodeling-based formation
oMBF: Overflow modeling based formation

Dempster et al. *J Clin Endocrinol Metab*. 2016;101(4):1353-1363

Results – Bone Formation from Baseline to 3 Months Within Groups



*<0.05; **<0.0001 for within group p-value by paired t-test

Dempster et al. *J Clin Endocrinol Metab*. 2016;101(4):1353-1363

ABALOPARATIDE

Research

JAMA | Original Investigation

Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis
A Randomized Clinical Trial

Paul D. Miller, MD; Gary Hattersley, PhD; Bente Juel Riis, MD; Gregory C. Williams, PhD; Edith Lau, MD; Luis Augusto Russo, MD, PhD; Peter Alexandersen, MD; Cristiano A. F. Zerbini, MD; Ming-yi Hu, PhD; Alan G. Harris, MD; Lorraine A. Fitzpatrick, MD; Felicia Cosman, MD; Claus Christiansen, MD; for the ACTIVE Study Investigators

IMPORTANCE Additional therapies are needed for prevention of osteoporotic fractures. Abaloparatide is a selective activator of the parathyroid hormone type 1 receptor.

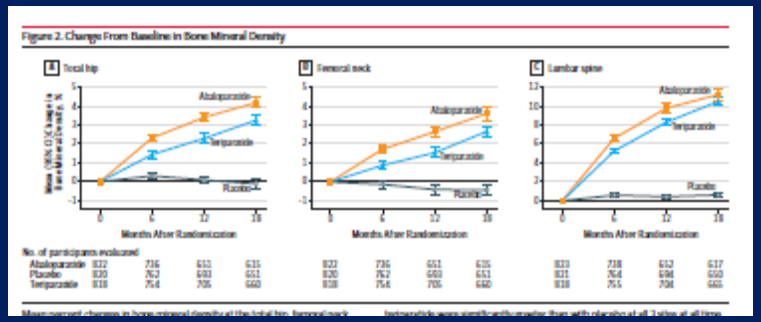
OBJECTIVE To determine the efficacy and safety of abaloparatide, 80 μg, vs placebo for prevention of new vertebral fracture in postmenopausal women at risk of osteoporotic fracture.

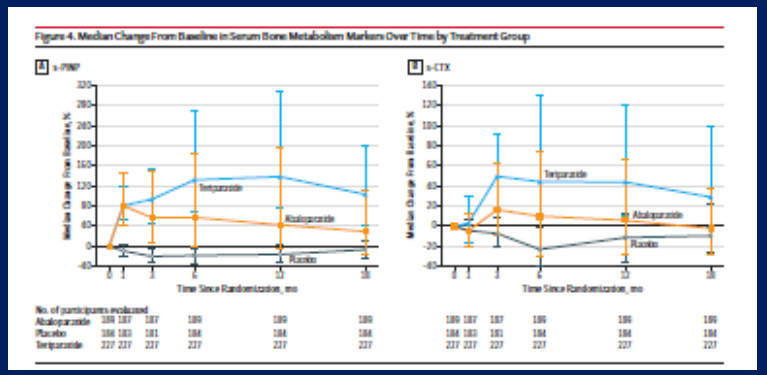
DESIGN, SETTING, AND PARTICIPANTS The Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) was a phase 3, double-blind, RCT (March 2011-October 2014) at 28 sites in 10 countries. Postmenopausal women with bone mineral density (BMD) T score ≤−2.5 and ≥−5.0 at the lumbar spine or femoral neck and radiological evidence ≥2 mild or ≥1 moderate lumbar or thoracic vertebral fracture or history of low-trauma nonvertebral fracture within the past 5 years were eligible. Postmenopausal women (≥65 y) with fracture criteria and a T score ≤−2.0 and ≥−5.0 or without fracture criteria and a T score ≤−3.0 and ≥−5.0 could enroll.

Editorial page 715

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com





Miller PD et al. JAMA. 2016 Aug 16;316(7):722-33

Bone 97 (2017) 314–319

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Effects of abaloparatide-SC (BA058) on bone histology and histomorphometry: The ACTIVE phase 3 trial☆

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ABSTRACT

There are a number of effective treatments for osteoporosis but most are in the antiresorptive class of compounds. Abaloparatide-SC is a new osteoanabolic agent, which increased bone mineral density and lowered the risk of osteoporosis-related fractures in the phase 3 ACTIVE trial. The objective of this report is to describe the effects of abaloparatide-SC 80 μg on bone histology and histomorphometry in iliac crest bone biopsies from this trial in which participants were randomized to receive blinded daily subcutaneous injections of placebo or abaloparatide-SC 80 μg/d or open-label teriparatide 20 μg/d for 18 months. Iliac crest bone biopsies were obtained between 12 and 18 months. Qualitative histological analysis of biopsies from abaloparatide-SC-treated patients revealed normal bone microarchitecture without evidence of adverse effects on mineralization or on the formation of normal lamellar bone. There were no bone marrow abnormalities, marrow fibrosis nor was there presence of excess osteoid or woven bone. There were few significant differences among the three treatment groups in a standard panel of static and dynamic histomorphometric indices. The mineral apposition rate was higher in the teriparatide-treated group than in the placebo-treated group. The eroded surface was lower in the abaloparatide-SC-treated group than in the placebo-treated group. Cortical porosity was higher in both the abaloparatide-SC- and the teriparatide-treated groups than in the placebo-treated group. We conclude that histological and histomorphometric analysis of iliac crest bone biopsies from subjects who were treated for up to 18 months with abaloparatide-SC showed no evidence of concern for bone safety.

Trial registration: ClinicalTrials.gov number NCT01343004.

ABALOPARATIDE: Bone Histomorphometry

Table 2
Histomorphometric variables in the 3 treatment groups.

Variable	Placebo (n=28)	Abaloparatide-SC (n=27)	Teriparatide (n=23)
Cancellous-bone volume/ total volume, %	17.26 (14.40, 22.03)	18.69 (15.88, 23.91)	19.83 (15.93, 25.52)
Trabecular thickness, μm	137.0 (108.0, 158.0)	138.0 (119.0, 152.0)	145.0 (126.0, 163.0)
Trabecular number, #/mm	1.34 (1.21, 1.53)	1.31 (1.18, 1.60)	1.37 (1.26, 1.71)
Trabecular separation, μm	735.5 (641.0, 816.0)	752.0 (614.0, 826.0)	715.0 (570.0, 782.0)
Wall thickness, μm	26.20 (24.00, 28.65)	27.60 (25.40, 29.60)	26.4 (25.00, 28.50)
Eroded surface/ bone surface, %	2.16 (1.25, 3.04)	1.06[b] (0.76, 2.19)	1.78 (1.07, 2.42)
Osteoid thickness, μm	5.70 (4.90, 6.35)	5.10 (4.30, 5.90)	5.40 (4.80, 6.20)
Osteoid volume, %	1.05 (0.39, 1.63)	0.59 (0.30, 1.35)	0.96 (0.44, 1.34)
Osteoid surface, %	8.03 (3.94, 12.38)	6.89 (3.58, 11.58)	10.55 (5.15, 14.06)
Mineralizing surface/ bone surface, %	5.43 (1.40, 8.77)	3.76 (0.75, 6.58)	3.23 (0.86, 9.89)
Mineral apposition rate, μm/d[a]	0.45 (0.39, 0.47)	0.49 (0.41, 0.54)	0.50[b] (0.44, 0.57)
Bone formation rate/ total volume, %/yr[a]	13.64 (6.90, 19.55)	10.93 (2.90, 19.29)	13.47 (6.65, 24.59)
Bone formation rate/ bone surface, $\mu m^3/\mu m^2/d$[a]	0.027 (0.014, 0.037)	0.020 (0.005, 0.036)	0.021 (0.013, 0.049)
Activation frequency, /yr [a]	0.390 (0.160, 0.540)	0.260 (0.070, 0.480)	0.270 (0.190, 0.650)
Adjusted apposition rate, μm/d[a]	0.240 (0.190, 0.390)	0.260 (0.120, 0.390)	0.250 (0.170, 0.500)
Formation period, d[a]	108.0 (63.0, 141.0)	111.5 (73.0, 176.0)	93.0 (51.0, 142.0)
Mineralization lag time, d[a]	23.40 (18.90, 26.70)	18.10 (14.60, 35.60)	20.10 (11.70, 44.00)
Cortical thickness, μm[c]	620.0 (405.0, 830.0)	681.0 (542.0, 839.0)	713.0 (433.0, 777.0)
Cortical porosity, %[c]	4.70 (4.10, 6.10)	5.80[b] (4.70, 7.50)	6.10[b] (4.70, 7.90)

Moreira CA, et al. Bone. 2017;97:314-319.

BMD Change in the Biopsy Cohort

Table 3
Bone mineral density at lumbar spine, femoral neck, and total hip at 18 months in the bone biopsy cohort.

	Placebo (n = 35)		Abaloparatide-SC (n = 36)		Teriparatide (n = 34)	
	Value (g/cm^2)	% change from BL	Value (g/cm^2)	% change from BL	Value(g/cm^2)	% change from BL
LS-BMD	0.855	0.49	0.960	12.45	0.943	9.70
	(0.136)	(4.72)	(0.139)	(7.95)[a,b]	(0.126)	(5.05)[a]
FN-BMD	0.747	-0.49	0.760	4.75	0.788	3.02
	(0.101)	(3.63)	(0.108)	(4.44)[a]	(0.086)	(3.64)[a]
TH-BMD	0.785	-0.42	0.802	4.40	0.826	3.10
	(0.096)	(2.41)	(0.093)	(3.98)[a]	(0.087)	(3.95)[a]

BL = baseline; BMD = bone mineral density; LS = lumbar spine; FN = femoral neck; TH = total hip. Values are expressed as the mean (SD); [a] $p<0.0001$ vs placebo. [b] $p = 0.0054$ vs teriparatide.

Potential Reasons for Lack of Differences

- Approximately 25% of the biopsies were not suitable for analysis (incomplete or fragmented cores)
- Biopsies performed at an average of 15 months on treatment – bone formation effect waning.
- Dr. Recker did not include biopsies with single labels in calculation of BFR (n=12)
- Apart from cortical thickness and porosity, no further analysis was performed on cortical bone. Teriparatide has larger effect on endocortex than in cancellous envelope
- However, the study served its purpose in demonstrating normal bone quality with abaloparatide treatment

EFFECTS OF ABALOPARATIDE ON MODELING AND REMODELING BASED BONE FORMATION

David W Dempster[1 2], Hua Zhou[1], Sudhaker D Rao[3], Chris Recknor[4], Paul Miller[5], Ben Leder[6], Miriam Annett[7], Bruce Mitlak[7]

ROMOSOZUMAB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Romosozumab Treatment in Postmenopausal Women with Osteoporosis

F. Cosman, D.B. Crittenden, J.D. Adachi, N. Binkley, E. Czerwinski, S. Ferrari, L.C. Hofbauer, E. Lau, E.M. Lewiecki, A. Miyauchi, C.A.F. Zerbini, C.E. Milmont, L. Chen, J. Maddox, P.D. Meisner, C. Libanati, and A. Grauer

ABSTRACT

BACKGROUND

Romosozumab, a monoclonal antibody that binds sclerostin, increases bone formation and decreases bone resorption.

Adapted from Cosman F, et al. *NEJM*. 2016;375:1532–1543.

Romozosumab - Histomorphometry

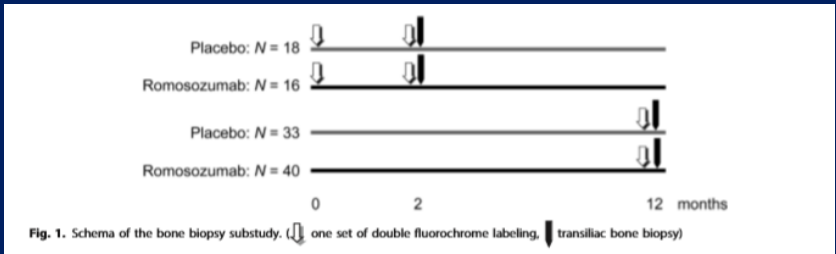
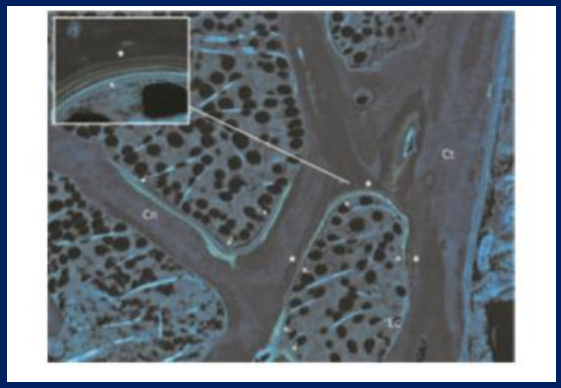


Fig. 1. Schema of the bone biopsy substudy. (⇩ one set of double fluorochrome labeling, ▮ transiliac bone biopsy)

Table 3. Static and Dynamic Bone Formation Parameters After 2 and 12 Months of Romosozumab

	Month 2			Month 12		
	Placebo N = 14	Romosozumab 210 mg QM N = 15	p value[a]	Placebo N = 31	Romosozumab 210 mg QM N = 39	p value[a]
Cancellous bone						
Cn-W.Th µm	31.7[b] (30.4, 33.9)	31.6 (30.7, 33.6)	0.91	29.5 (27.8, 32.3)	31.8 (30.8, 34.1)	0.014
Cn-OS/BS %	7.2 (1.7, 15.5)	14.2 (9.4, 24.3)	0.058	7.8 (3.7, 15.4)	4.4 (2.8, 9.0)	0.16
Cn-OV/BV %	1.3 (0.2, 1.9)	3.0 (1.4, 5.4)	0.007	1.7 (0.8, 4.5)	0.8 (0.4, 1.7)	0.016
Cn-O.Th µm	8.6 (6.9, 9.5)	9.7 (9.0, 12.6)	0.029	9.9 (8.5, 12.5)	9.7 (8.6, 11.0)	0.57
Cn-MAR[c] µm/day	0.65 (0.54, 0.70)	0.57 (0.50, 0.59)	0.097	0.54 (0.50, 0.61)	0.48 (0.36, 0.55)	0.015
Cn-MAR[d] µm/day	0.65 (0.54, 0.70)	0.57 (0.50, 0.59)	0.097	0.55 (0.50, 0.61)	0.49 (0.41, 0.58)	0.047
Cn-MS/BS %	2.3 (0.7, 3.1)	5.6 (3.7, 8.4)	0.002	3.0 (0.9, 5.4)	0.6 (0.0, 2.2)	0.004
Cn-BFR/BS[c] $\mu m^3/\mu m^2$/year	5.175 (2.919, 7.165)	12.075 (7.319, 16.132)	0.004	6.755 (2.691, 13.213)	1.577 (0.928, 6.452)	0.014



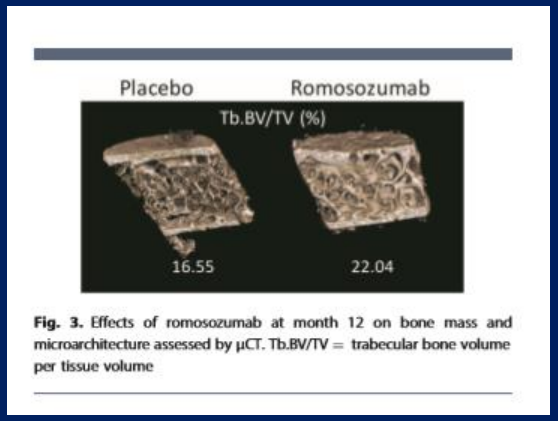
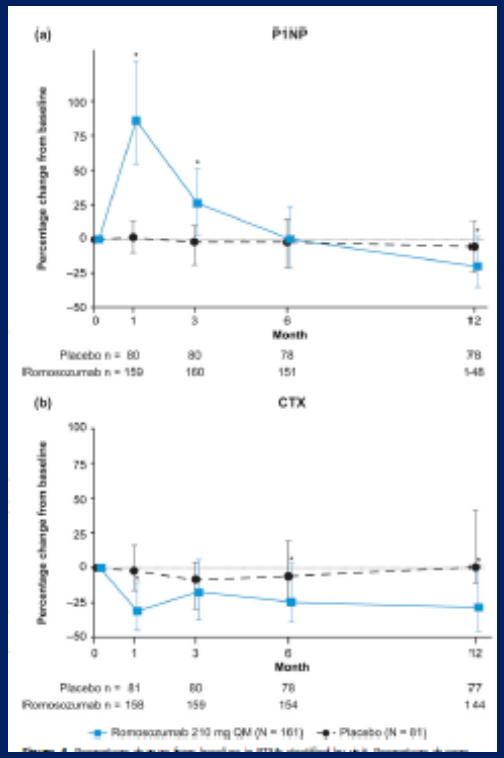


Fig. 3. Effects of romosozumab at month 12 on bone mass and microarchitecture assessed by µCT. Tb.BV/TV = trabecular bone volume per tissue volume

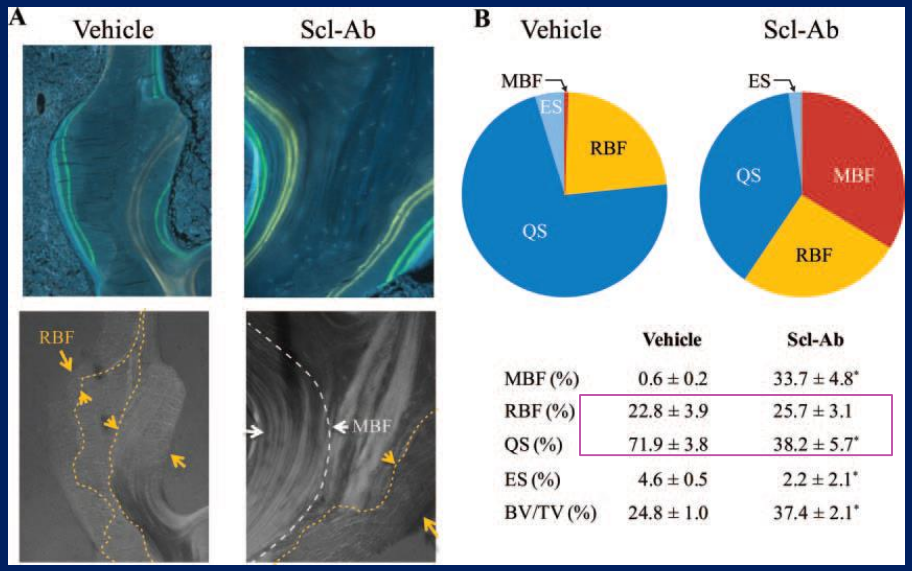
Chavassieux et al, J Bone Miner Res. 2019 Sep;34(9):1597-1608

Romosozumab – Biochemical Markers



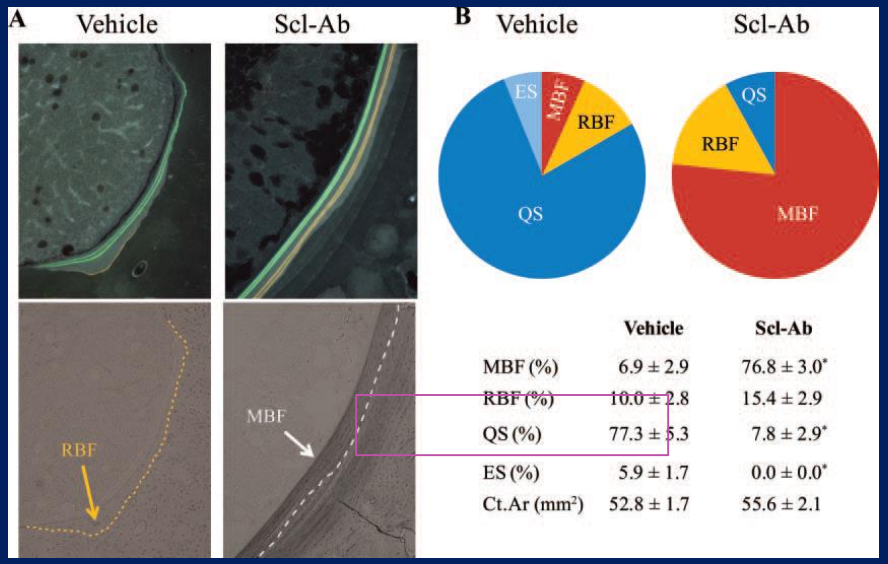
Lewiecki EM, et al J Clin Endocrinol Metab. 2018 Sep 1;103(9):3183-3193.

Modeling in Monkeys Treated with Sclerostin Antibody



	Vehicle	Scl-Ab
MBF (%)	0.6 ± 0.2	33.7 ± 4.8*
RBF (%)	22.8 ± 3.9	25.7 ± 3.1
QS (%)	71.9 ± 3.8	38.2 ± 5.7*
ES (%)	4.6 ± 0.5	2.2 ± 2.1*
BV/TV (%)	24.8 ± 1.0	37.4 ± 2.1*

Trabecular Envelope

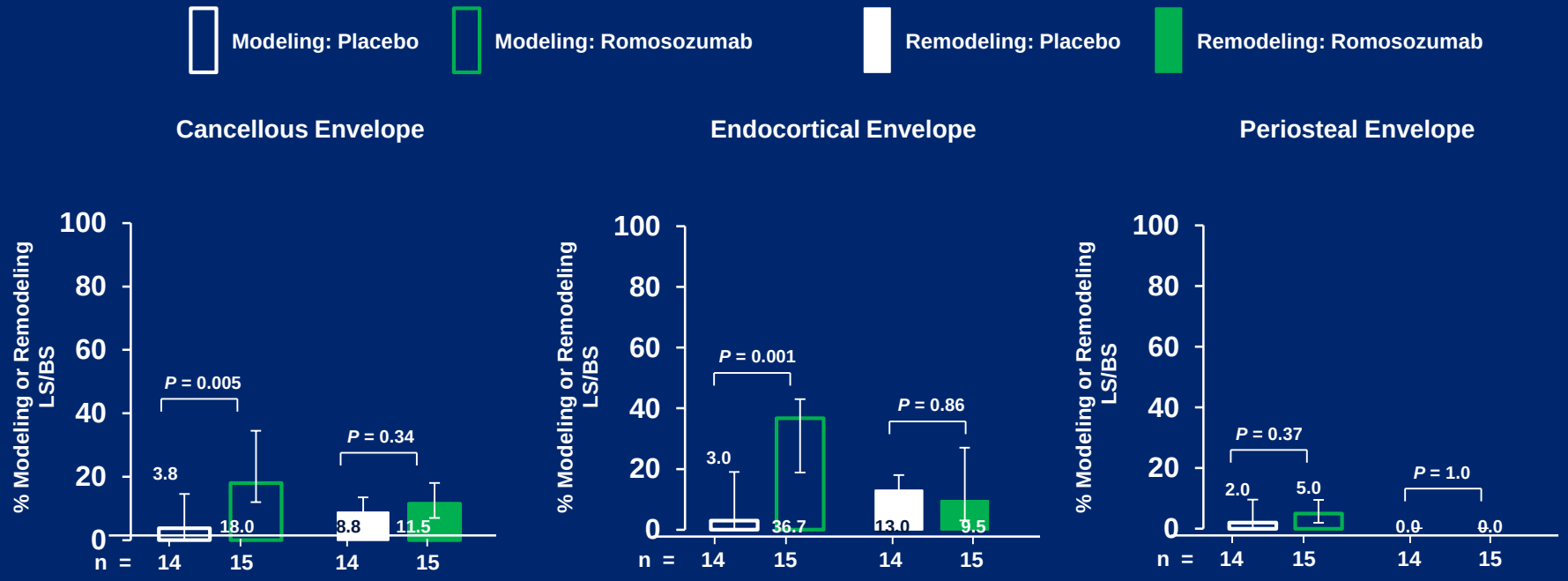


	Vehicle	Scl-Ab
MBF (%)	6.9 ± 2.9	76.8 ± 3.0*
RBF (%)	10.0 ± 2.8	15.4 ± 2.9
QS (%)	77.3 ± 5.3	7.8 ± 2.9*
ES (%)	5.9 ± 1.7	0.0 ± 0.0*
Ct.Ar (mm²)	52.8 ± 1.7	55.6 ± 2.1

Endocortical Envelope

Ominsky et al, J Bone Miner Res. 2014 Jun;29(6):1424-30.

Bone Modeling and Remodeling After 2 Months of Romosozumab vs Placebo



Data are median (Q1, Q3). n = Number of subjects with evaluable histomorphometry data at the timepoint of interest. Nominal *P*-values are the treatment difference (romosozumab vs placebo) and are based on the Wilcoxon rank-sum test without multiplicity adjustment. BS, bone surface; LS, labeled surface.

Eriksen et al, ASBMR, Orlando, FL,2019

Summary

Anabolic agents improve cancellous and cortical bone microarchitecture.

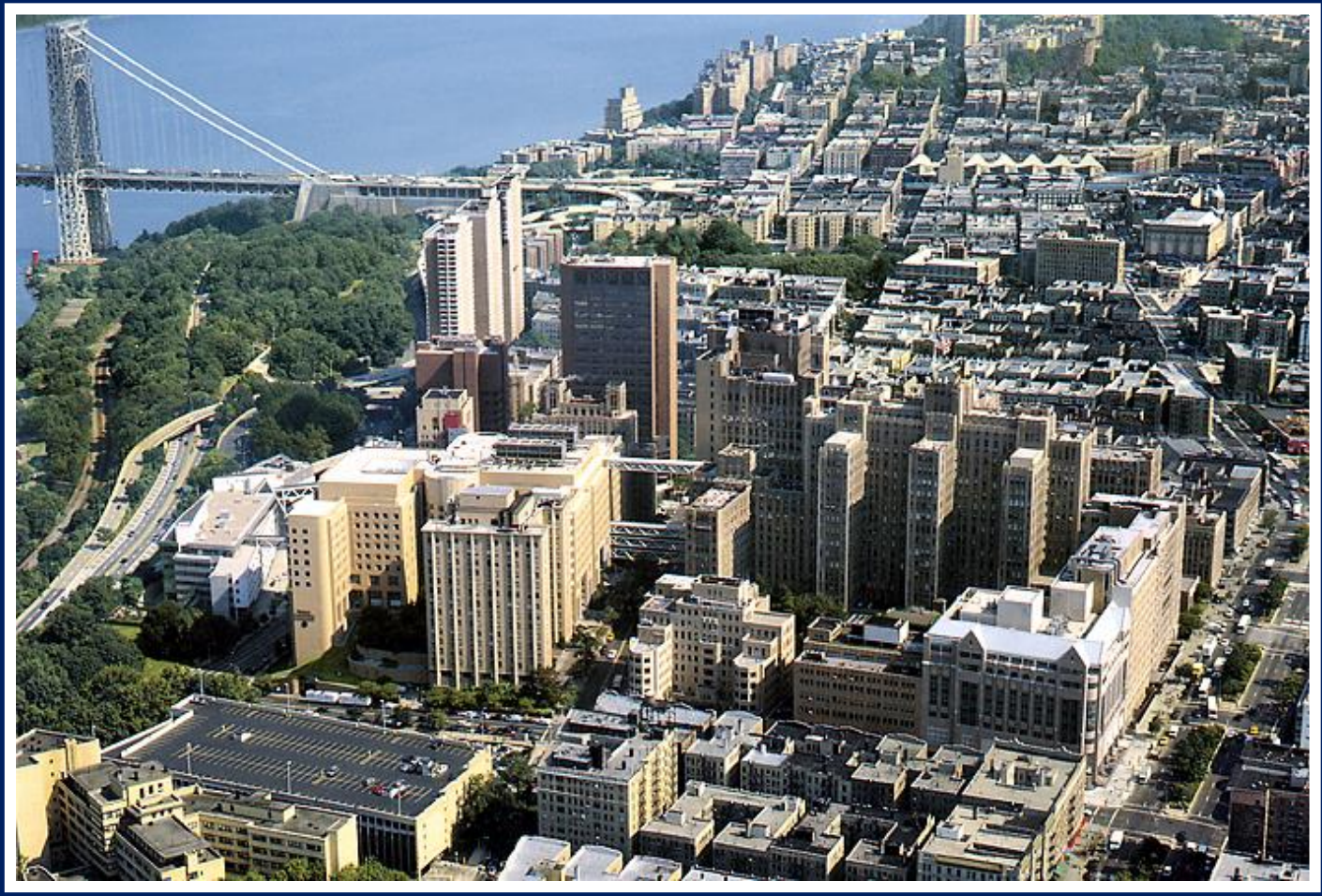
PTH-1 receptor agonists (teriparatide and abaloparatide) stimulate resorption and formation (formation > resorption). New bone formation occurs primarily by remodeling-based bone formation, but there is also some stimulation of modeling-based bone formation.

Sclerostin antibodies (romosozumab) stimulate bone formation and simultaneously inhibit bone resorption. New bone formation occurs primarily by modeling-based bone formation.

Recent head-to-head fracture trials (teriparatide vs. residronate; romosozumab vs. alendronate indicate that anabolic drugs offer superiopr fracture protections than antiresorptive drugs.

The fundamentally different mechanisms of action and recent fracture trials support the sequential use of anabolic and antiresorptive drugs.

Thank You!



College of Physicians and Surgeons of Columbia University, New York