# ASBMR 2021

# Cortical Thickness and Bone Material Properties are Related to Fragility Fracture in Post-Menopausal Women with Normal Bone Mineral Density

*Donald Kimmel, Anastasia Desyatova, Joseph Turner, Mohammed Akhter, Joan Lappe, Robert Recker. Creighton University, United States, University of Nebraska (Omaha), United States, University of Nebraska (Lincoln), UnitedStates

- Two groups of post-menopausal women with:
- fragility fracture subjects (N=60) and age/BMD-matched, non-fragility fracture subjects (N=60).
- Normal(T-Score> -0.99) and Osteopenic (T-Score<=-1.0) BMD cohorts were designated within both the fracture and non-fracture groups.
- Transiliac biopsy specimens were obtained to evaluate dynamic histomorphometric and microarchitectural (MicroCT) endpoints and
- Bone material properties by quasi-static and dynamic nanoindentation testing
- CONCLUSION Post-menopausal women with normal BMD and fragility fracture display lower cortical thickness and lower heterogeneity of the bone tissue strength endpoints, hardness, modulus, and storage modulus, in cortical mineralized bone tissue.
- Cortical thickness is an established risk factor for fragility fracture in osteoporotic women that tends to be BMD-independent.
- Lower heterogeneity in a material offers less resistance to the propagation of microcracks, causing the material to have less resistance to fracture.

**Selected Variables from Non-fracture and Fracture Normal BMD Women**

| | Non-Fx | Fx | |
|---|---|---|---|
| Variable | Med | Med | P= |
| Age (yrs) | 59.7 | 59.5 | 0.9590 |
| Total Hip T-Score | -0.53 | -0.39 | 0.1378 |
| Body Mass Index (kg/m$^2$) | 26.6 | 25.5 | 0.7047 |
| Iliac Cortical Thickness (µm) | 835 | 736 | 0.0041 |
| Cortical Hardness (variance) | 0.110 | 0.080 | 0.0068 |
| Cortical Modulus (variance) | 2.22 | 1.45 | 0.0009 |
| Cortical SM (variance) | 2.01 | 1.55 | 0.0054 |

Med- Median; Fx-Fracture; P= Wilcoxon Signed Rank Test; SM- Storage Modulus

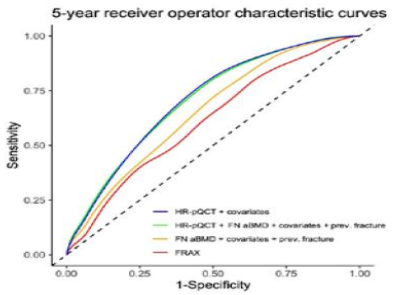
- -Δυναμική Ιστομορφομετρια
- -MicroCT
- -Nanoidentation

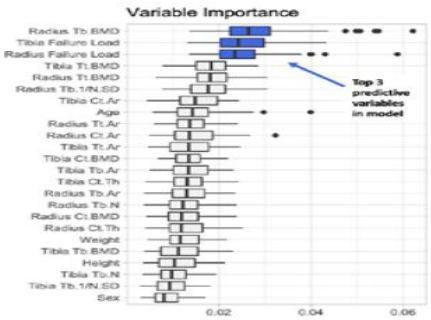
Οι Μετεμμηνοπαυσιακες γυναίκες με φυσιολογική ΟΠ και κατάγματα έχουν ---
-χαμηλότερο πάχος φλοιού
-μικρότερη ετερογένεια της επιμεταλλωσης
- και επηρεασμένους διάφορους Δείκτες της ποιότητας του οστού .

# A fracture risk assessment tool for high resolution peripheral quantitative computed tomography: The Bone Microarchitecture International Consortium (BoMIC)

*Danielle Whittier, Elizabeth Samelson, Marian Hannan, Emmanuel Biver, Pawel Szulc, Elisabeth Sornay-Rendu, Roland Chapurlat, David Goltzman, Sundeep Khosla, Serge Ferrari, Mary Bouxsein, Doug Kiel, Steven Boyd.

- The majority of fragility fractures occur in people who are not osteoporotic based on femoral neck (FN) areal bone mineral density (aBMD).
- Although there are well-established clinical tools that provide fracture risk assessment using clinical risk factors, stratification of fracture risk remains a challenge
- HR-pQCT holds promise because it provides novel information about bone density and structure.
- This study proposes a new fracture risk assessment tool based on HR-pQCT to provide a 5-year risk of major osteoporotic fracture (MOF).
- Participants included 6,802 individuals (71% female) with HR-pQCT data from the Bone Microarchitecture International Consortium, a prospective multicenter cohort.
- Participants were between 40 – 96years and were followed for incident MOF (wrist, hip, spine, humerus).
- Mean follow-up was 4.7 +/- 2.4 years
- Conclusion: A fracture risk assessment tool using HR-pQCT has been developed and demonstrated to outperform current clinical metrics for assessing fracture risk.




- **Προοπτική πολυκεντρική μελέτη 6,802 ατόμων με HRpQCT**
- **40-96 ετών**
- **Μέσος χρόνος παρακολούθησης 4.7 έτη**

- **Διάφοροι δείκτες της Μικροαρχιτεκτονικης του οστού όπως ελέγχονται με HRpQCT αποδεικνύονται οι ανώτεροι προγνωστικοί παράγοντες για 5ετη κίνδυνο μείζονος Οστεοπορωτικου κατάγματος σε σύγκριση:**
- **-Μοντέλο ΟΠ Αυχ.Μηριαιου+Καταγμα**
- **-FRAX**

# Age at menopause as predictor of bone mineral density and fracture risk in postmenopausal women: results from SWAN

*Albert Shieh, Kristine Ruppert, Gail Greendale, Yinjuan Lian, Jane Cauley, Sherri-Ann Burnett-Bowie, Carrie Karvonen-Gutierrez, Arun Karlamangla. UCLA Health, United States, University of Pittsburgh, United States, MGH, United States, University of Michigan, United States

- This study was conducted in the Study of Women's Health Across the Nation, a longitudinal study of the menopause transition in a diverse cohort of ambulatory women.
- Conclusions: Years since the FMP is more strongly associated with lower postmenopausal BMD than chronological age, and earlier menopause is associated with more fractures.
- Years since the FMP may need to replace chronological age in extant fracture prediction tools

Table
Associations of time elapsed since the final menstrual period with postmenopausal BMD, and age at menopause with incident fracture

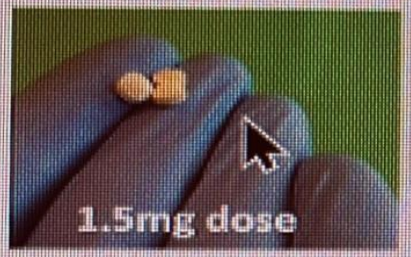
| | Associations[a] of time elapsed since the final menstrual period (FMP) with postmenopausal BMD | | | |
|---|---|---|---|---|
| | Lumbar spine (g/cm$^2$) | p-value | Femoral neck (g/cm$^2$) | p-value |
| Time from FMP (years) | -0.009 (-0.012, -0.005) | <0.0001 | -0.005 (-0.007, -0.002) | 0.0001 |
| Chronological age (years) | 0.007 (0.003, 0.011) | 0.0003 | -0.000 (-0.003, 0.002) | 0.8 |
| | | | | |
| | Association[b] of age at FMP with incident fracture | | | |
| | Hazard ratio for incident fracture (95% CI) | | | p-value |
| Age at FMP (years) | 0.95 (0.91, 0.99) | | | 0.02 |

- Τα έτη από την τελευταία έμμηνο ρύση και όχι η χρονολογική ηλικία σχετίζονται με την μετεμηνοπαυσιακή οστική απώλεια και η πρώιμη εμμηνόπαυση με αυξημένο κίνδυνο κατάγματος
- Τα ετη από την τελευταία έμμηνο ρύση πρέπει να αντικαταστήσουν την χρονολογική ηλικία σαν παράγοντα κινδύνου κατάγματος

**A Six-month Phase 2 Study of Oral PTH in Postmenopausal Women with Low Bone Mass** Liana Tripto-Shkolnik,Auryan Szalat, Gloria Tsvetov, Vanessa Rouach, Chana Sternberg, PhillipSchwartz, Anke Hoppe, Gregory Burshtein, Lital Friedman, Hillel Galitzer,Arthur Santora.

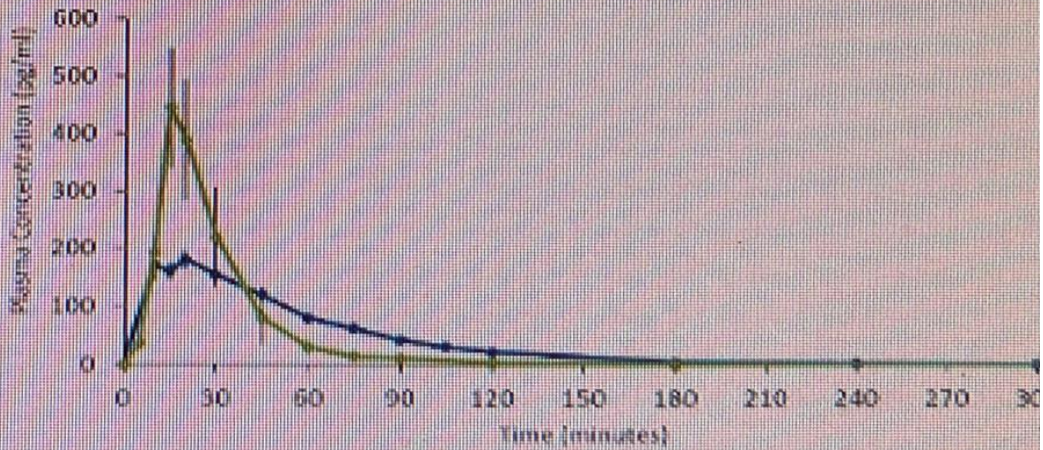
## Background

- EBP05 is an oral formulation of hPTH(1-34), based on the proprietary drug delivery technology which promotes enteric absorption and stabilizes the teriparatide in the gastrointestinal tract





*Pharmacokinetics of 1.5mg oral PTH(1-34) formulation (EBP05) and of Forteo® 20ug in healthy volunteers (n=9) (mean±SE)*




*Data presented at ASBMR 2013 Annual Meeting: "An oral PTH(1-34) formulation with a pharmac profile optimized for the treatment of osteoporosis", Gregory Bandstein, Hillel Galitzer, Ariel Rot Phillip Schwartz, Roger Garceau, Eric Lang, Jonathan C. Y. Tang, William D. Fraser, Joseph Cora*

# Study Design

- A Phase 2, 6-month, randomized, dose-ranging, placebo-controlled study
- Conducted at 4 sites in Israel between June 2019 and May 2021

## Screening

**Key inclusion criteria**

- >50 yr old and >3+ yr post menopause
- BMD T-score ≤ -2; >-3.5

**Key exclusion criteria**

- Osteoporosis treatment within last 2 yr
- Other disorders of bone or mineral metabolism
- Severe osteoporosis that precludes placebo

## Endpoints

**Primary – at 3 months**

- Serum P1NP change from baseline at 3 months

**Secondary – at 6 months**

- BMD change from baseline at 6 months
- P1NP, Osteocalcin, Bone Alkaline Phosphatase
- Serum CTX, Urine NTX/Creatinine
- Plasma hPTH(1-34) at $T_{15\ min}$

# Study Design

- A Phase 2, 6-month, randomized, dose-ranging, placebo-controlled study
- Conducted at 4 sites in Israel between June 2019 and May 2021

**Treatment – Oral PTH**

Randomization N=161

Arm 1: Placebo tablets QD

Arm 2: 0.5 mg *

Arm 3: 1.0 mg *

Arm 4: 1.5 mg QD

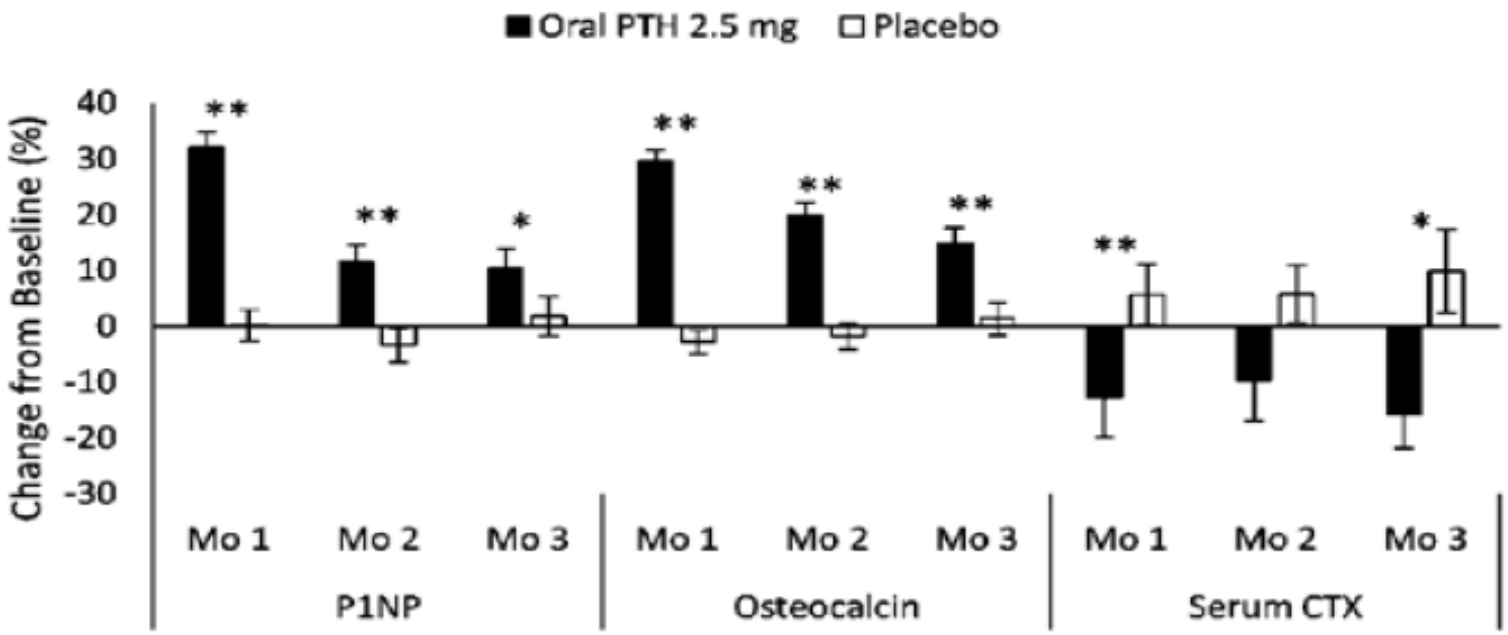
Arm 5: 2.5 mg QD * **

Arm 6: 2.5mg titrated QD **

* Following an interim analysis, a 2.5mg arm was added and recruitment to the 0.5mg & 1.0 mg arms was stopped

** Following AEs typical of orthostasis additional subjects in the 2.5mg group received 1.5mg for 1 month, 2.0mg for the next

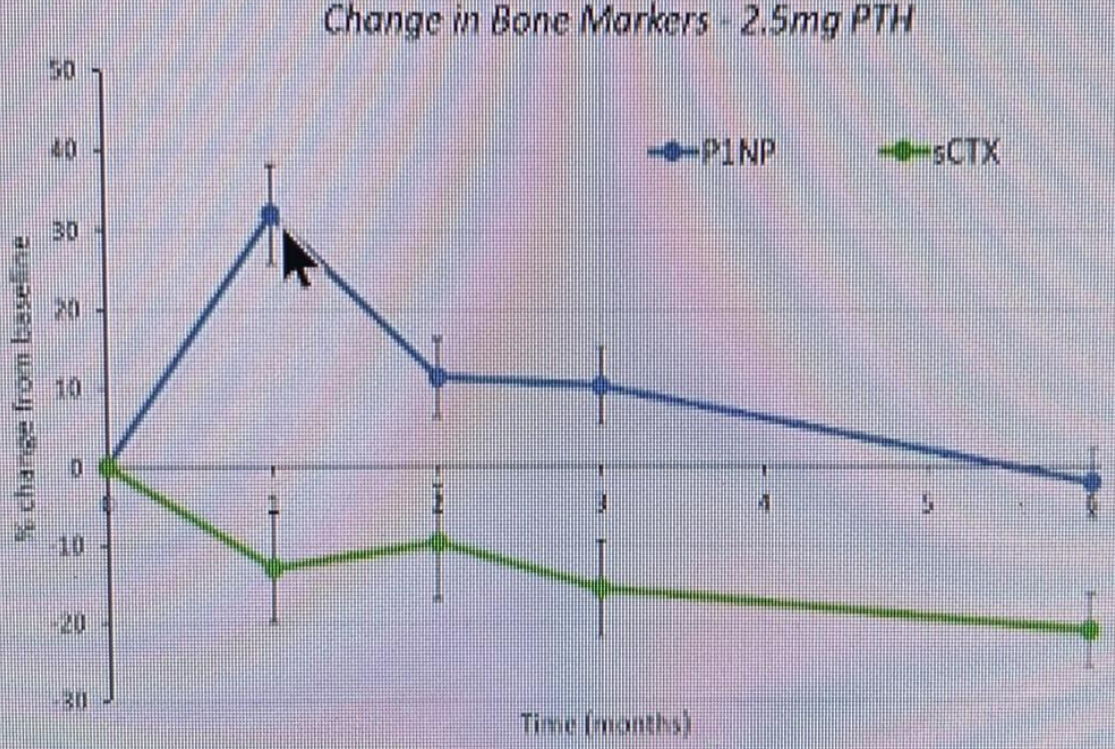
## Bone Biomarker Percent Change from Baseline with Daily Oral hPTH(1-34) 2.5 mg (Mean and SE)




* p< 0.05 vs. Placebo; ** p< 0.01 vs. Placebo

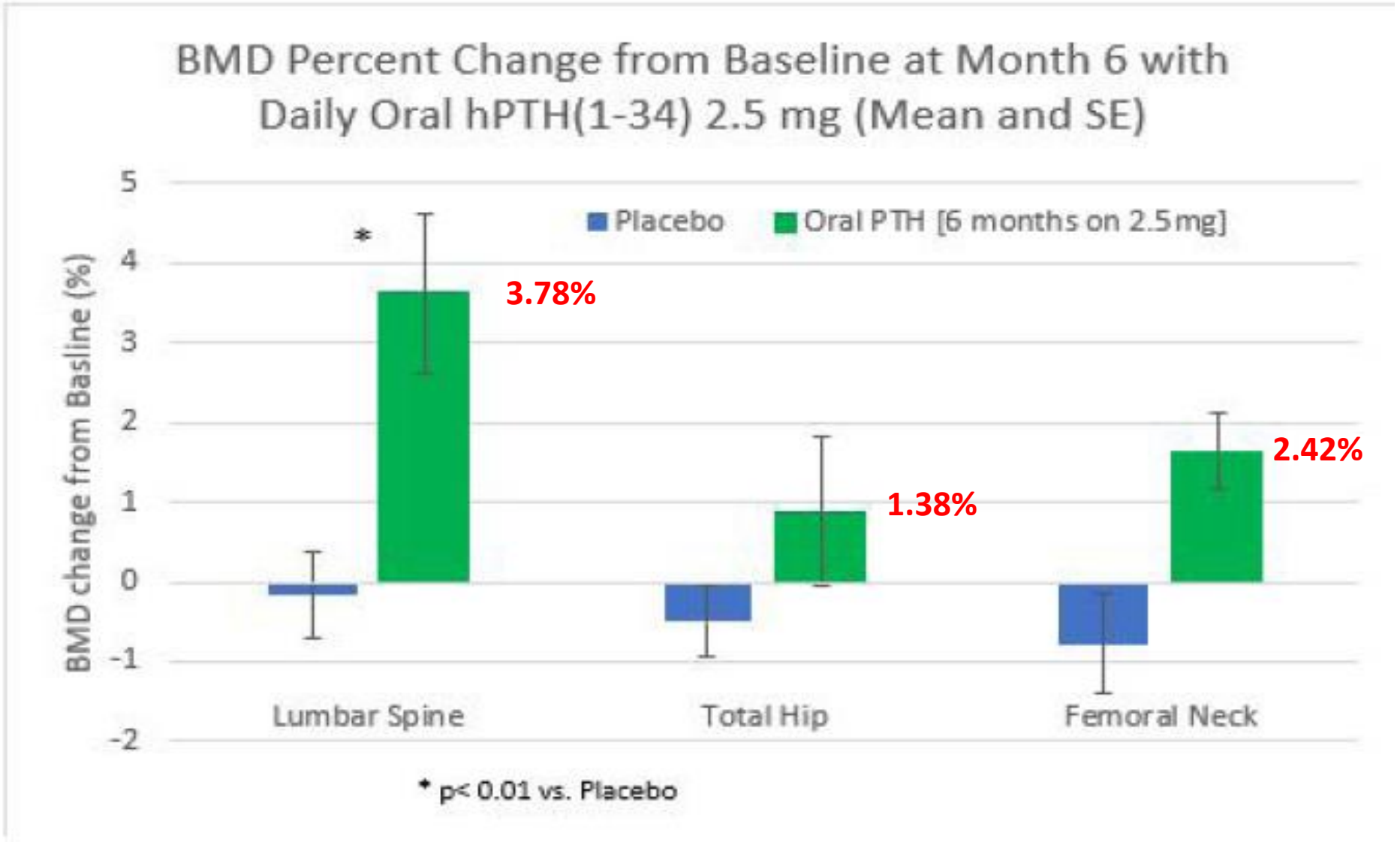
# 6 Months Bone Markers Results

- In the 2.5 mg PTH group, Serum CTX decreased 21% from baseline at **6 months** ($p < 0.01$) while P1NP was unchanged




* Biomarker data for Months 1-3 previously presented as a poster – ASBMR 2021 Preliminary Poster FRI 237

# BMD


BMD Percent Change from Baseline at Month 6 with Daily Oral hPTH(1-34) 2.5 mg (Mean and SE)
BMD change from Basline (%)
5
4
3
2
1
0
-1
-2
Placebo
Oral PTH [6 months on 2.5mg]
*
3.78%
1.38%
2.42%
Lumbar Spine
Total Hip
Femoral Neck
* p< 0.01 vs. Placebo

# Safety Results

- The safety profile of oral PTH was consistent with the known profile of subcutaneous PTH
- AEs commonly attributed to vasodilatation with subcutaneous PTH were observed - headache, nausea, presyncope and dizziness*.
- There were no serious drug-related AEs
- Mean serum calcium and changes exceeding PDLC were not increased and there were no treatment-emergent Hypercalcemia AEs

| Subject disposition | Placebo (N=43) | | EB105 0.5 mg orally QD (N=25) | | EB105 1 mg orally QD (N=29) | | EB105 1.5 mg orally QD (N=28) | | EB105 2.5 mg orally QD (N=19) | | EB105 2.5 mg titrated orally QD (N=17) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % | N | % |
| Randomized | 43 | 100 | 25 | 100 | 29 | 100 | 28 | 100 | 19 | 100 | 17 | 100 |
| Discontinued Before Month 3 | 3 | 7 | 3 | 12 | 2 | 6.9 | 4 | 14.3 | 7 | 36.8 | 1 | 5.9 |
| Discontinued from Study Before Month 6 | 5 | 11.6 | 3 | 12 | 3 | 10.3 | 6 | 21.4 | 9 | 47.4 | 1 | 5.9 |

# Conclusions

**In this study of postmenopausal women with osteoporosis or low BMD, Six months of treatment with oral PTH 2.5 mg:**

- Increased lumbar spine, femoral neck and total hip BMD compared to placebo, and compared to start of treatment
- The increase in spine BMD was similar in magnitude to that previously reported with Forteo®
- Increases in total hip and femoral neck were greater than those previously reported with Forteo®
- Reduced serum CTX compared to placebo
- Adverse event profile similar to that observed with Forteo®, and typical of orthostatic hypotension
- Was not associated with serum calcium increases or Hypercalcemia Adverse Events
- Greater than 90% of subjects tolerated the 2.5 mg dose well, after titration starting with the 1.5, and progressing through 2.0 mg doses

**Circulating sclerostin levels are positively related to coronary artery disease severity and related risk factors** *Monika Frysz, Ingrid Gergei, Hubert Scharnag, George Davey Smith, Jie Zheng, Deborah Lawlor, Markus Herrmann, Winfried Maerz, Jon Tobias.

- in the present study, we examined relationships between **serum sclerostin and CVD and related risk factors**,
- **in the Ludwigshafen Risk and Cardiovascular Health (LURIC**=was designed to investigate environmental and genetic risk factors for the development of cardiovascular diseases) and
- **Avon Longitudinal Study of Parents and Children (ALSPAC**= is a prospective birth cohort that recruited pregnant women with expected delivery dates between April 1991 and December 1992 from Bristol, UK. The present study uses data from a research clinic undertaken between 2008 and 2011), together providing over 5000 participants.

Table 4: Sclerostin versus CVD disease outcomes (ALSPAC/LURIC)

| | LURIC (N=2054) | | | |
|---|---|---|---|---|
| **Exposure** | **Outcome** | **Model** | **β (95% CI)** | **p** |
| Sclerostin | Friesinger Score | 1 | 0.14 (0.09,0.18) | <0.001 |
| Sclerostin | Friesinger Score | 2 | 0.05 (0.01,0.09) | 0.018 |
| Sclerostin | Friesinger Score | 3 | 0.03 (-0.02,0.07) | 0.252 |
| | | | **HR (95% CI)** | **p** |
| Sclerostin | Death from cardiac cause | 1 | 1.21 (1.14,1.28) | <0.001 |
| Sclerostin | Death from cardiac cause | 2 | 1.13 (1.03,1.23) | 0.007 |
| Sclerostin | Death from cardiac cause | 3 | 1.03 (0.93,1.15) | 0.557 |
| | | | **OR (95% CI)** | **p** |
| Sclerostin | Coronary artery stenosis* | 1 | 1.47 (1.29,1.67) | <0.001 |
| Sclerostin | Coronary artery stenosis* | 2 | 1.16 (1.02,1.32) | 0.026 |
| Sclerostin | Coronary artery stenosis* | 3 | 1.09 (0.96,1.24) | 0.189 |
| | | | | |
| | **ALSPAC (N=3015)** | | | |
| | **Outcome** | | **β (95% CI)** | |
| Sclerostin | cIMT | 1 | 0.06 (0.03,0.10) | 0.001 |
| Sclerostin | cIMT | 2 | 0.02 (-0.02,0.05) | 0.409 |
| Sclerostin | cIMT | 3 | 0.01 (-0.02,0.05) | 0.550 |
| Sclerostin | Av. Distensibility | 1 | -0.02 (-0.05,0.02) | 0.328 |
| Sclerostin | Av. Distensibility | 2 | 0.02 (-0.01,0.06) | 0.183 |
| Sclerostin | Av. Distensibility | 3 | 0.03 (-0.01,0.07) | 0.106 |

Table shows results of linear/logistic/cox proportional hazards regression analysis. Results are SD change in outcome/ odds/ HR of outcome per SD increase in sclerostin, 95% CI and p value. CI: Confidence Interval, HR: Hazard ratio. cIMT: carotid intima media thickness. Model 1: unadjusted; Model 2: adjusted for age and ethic group (ALSPAC) and sex (LURIC), BMI, smoking, social deprivation, Model 3: Model 2 plus LDL and HDL cholesterol, log triglycerides, diabetes, hypertension, eGFR, Apolipoprotein A-I.

- Higher sclerostin levels were associated with higher risk of diabetes mellitus (DM) [1.25 (1.12, 1.37)],
- risk of elevated fasting glucose [1.15 (1.04, 1.26)],
- and triglyceride levels [0.03 (0.00, 0.06)].
- with lower eGFR [-0.20 (-0.38, -0.02)],
- HDL cholesterol [-0.05 (-0.10, -0.01)],
- and Apolopoprotein A-I [-0.05 (-0.08, -0.02)]

Contrary to trial evidence suggesting sclerostin inhibition leads to an increased risk of CVD, sclerostin levels appear to be positively associated with CAD severity and mortality, partly explained by a relationship between higher sclerostin levels and major CVD risk factors.

**Clinical Characteristics, Including History of Myocardial Infarction and Stroke, Among US PMO Women Initiating Treatment with Romosozumab and Other Anti-osteoporosis Therapies** *Carrie Nielson, Tzu-Chieh Lin, Mary Oates, Cynthia Deignan, Zhigang Yu.

- This study is an ongoing USFDA post-marketing requirement (2020-2024) to assess the impact of boxed warning on romosozumab (romo) treatment and the feasibility of future comparative safety analysis using real-world data.
- Women at least 55 yrs old who had newly initiated romo, denosumab (dmab), zolendronate (zol), PTH analogues, or oral bisphosphonates (BPs) were included.
- As of March 2021,about 14,958 person-years of exposure to romo have been reported in US.

# RESULTS

- Patients newly initiating romo (N=1,946; mean age 74.8 yr) were older than zol (N=6,292; 72.9 yr), PTH (N=1,517; 70.7 yr), and oral BPs (N=38,544; 72.1 yr).
- Romo patients had increased prevalence of chronic diseases (eg, hypertension, hyperlipidemia, typeII DM) and healthcare utilization, and had more prior fractures and OP treatments.
- **Using all available historical data**, the proportion of patients with MI/stroke history was higher in romo patients (9%/11.5%) than dmab (6.8%/8.6%), PTH (7.4%/9.0%), zol(5.9%/7.0%) and oral BPs (5.4%/6.0%)
- When limited to 1 yr before treatment initiation, the proportions of patients with MI/stroke in romo were very low (MI: 0.4%,N=8; stroke: 0.5%, N=9) and similar to other OP treatments.
- Conclusions: Patients who initiated romo were a high OP-risk population and generally had more comorbidities including CV risk factors. Nevertheless, the low proportion of patients who had a MI/stroke within 1-yr prior to treatment initiation suggests the label boxed warning language may have had the intended effect on patient selection

- Οι ασθενείς που ξεκίνησαν θεραπεία με ROMO ηταν μεγαλύτερης ηλικίας ,είχαν αυξημένο κίνδυνο κατάγματος, και γενικά είχαν πολλές συννοσηρότητεςσυμπεριλαμβανομένων διαφόρων παραγόντων καρδιαγγειακού κινδύνου.
- Αυξημένο γενικά ιστορικο Ε/ΑΕΕ σε σύγκριση με τα άλλα φάρμακα
- Το χαμηλό ποσοστό ασθενών με ιστορικό Ε/ΑΕΕ 1 ετοςπριν την έναρξη αγωγής με ROMO δείχνει ότι η προειδοποίηση βοηθά στην κατάλληλη επιλογή ασθενών για θεραπεία

# Radiofrequency Echographic Multi Spectrometry (REMS)

**New technology REMS for bone evaluation compared to DXA in adult women for the osteoporosis diagnosis: a real-life experience** *Débora Meira Ramos Amorim1, Eliane Naomi Sakane1, Sergio Setsuo Maeda1, Marise Lazaretti Castro1. 1Federal University of Sao Paulo, Brazil

- Purpose: to assess the accuracy of REMS technology in diagnosing osteoporosis in comparison with Dual X-ray absorptiometry (DXA) on a population of Brazilian women.
- The REMS accuracy for the osteoporosis diagnosis was evaluated in comparison with DXA on both sites (Spine-Hip)
- A total of 343 patients were enrolled in the study(women age ranged between 30-80).
- there were not cases diagnosed as osteoporosis by DXA that were defined as normal by REMS.
- The REMS intra-operator CV was 0.51% for the lumbar spine and 1.08% for the femoral neck.
- The REMS inter-operator CV was 1.43% for the lumbar spine and 1.93% for the femoral neck

**Identification of Bone Fragility: Use of Fragility Score measured by Radiofrequency Echographic Multi Spectrometry (REMS) at Femoral Neck**

*Francesco Conversano1, Paola Pisani1, Delia Ciardo1, Fiorella Anna Lombardi1, Ernesto Casciaro1, Roberto Franchini1, Sergio Casciaro1. 1National Research Council, Institute of Clinical Physiology, Italy

- The Fragility Score (FS) assessed REMS is a measure of bone fragility, ranging from 0 to 100 (100 corresponds to maximum fragility).
- With this study, the performance of the FS, assessed by femoral neck REMS scans, in discriminating patients with or without incident hip fractures has been evaluated. The results were also compared with the ones obtained by T-score values measured by Dual-energy X-ray Absorptiometry (DXA) and by REMS.
- Conclusion: This study showed that the FS measured through a REMS femoral neck scan effectively discriminates between patients with and without incident fragility fractures at the hip, with performance superior than the ones observed for T-score values

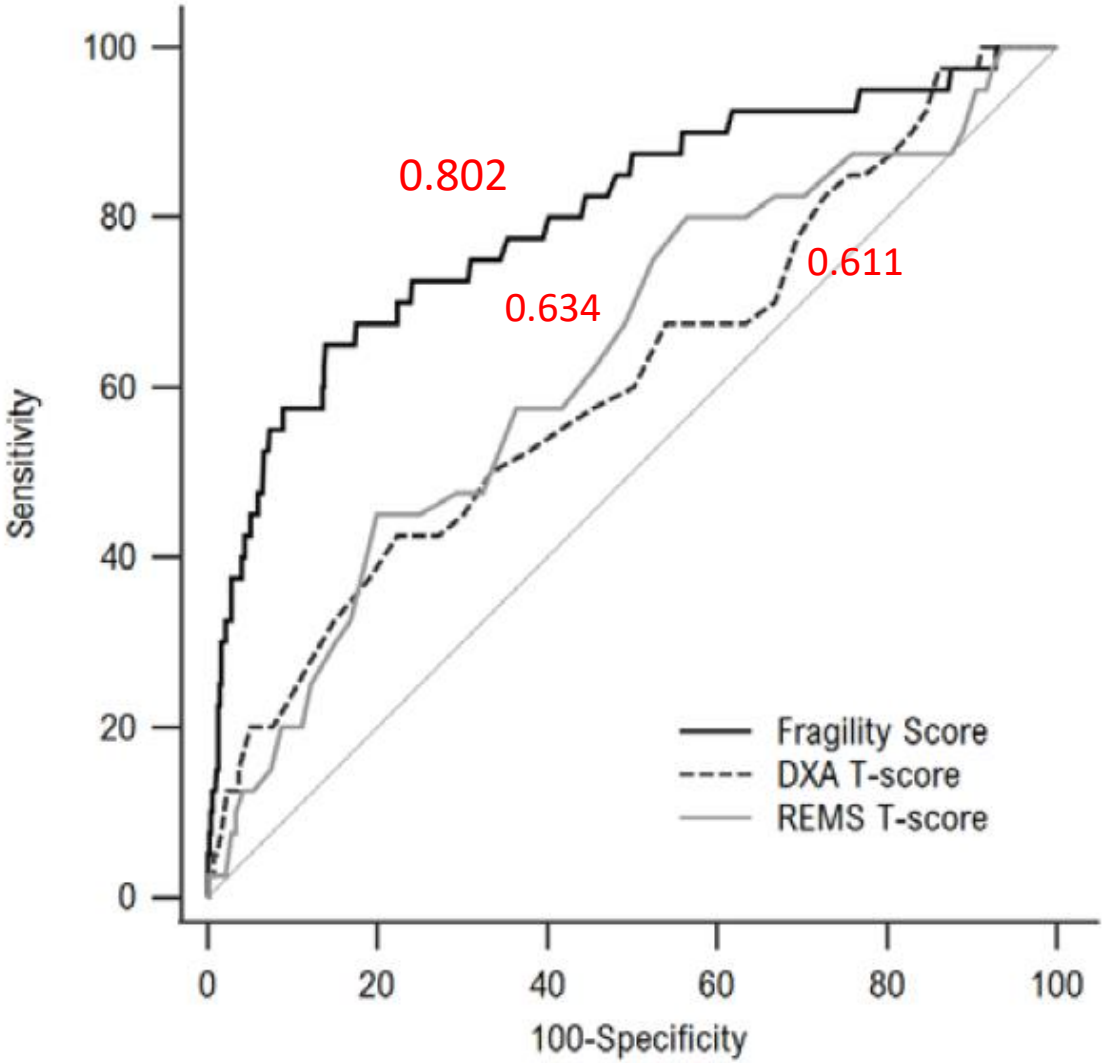



**Figure 1** – ROC curve analysis evaluating the ability to discriminate between patients who sustained or not an incident fragility fracture at the hip.

# Prevalence of Monoclonal Gammopathy of Undetermined Significance in Patients Presenting with Vertebral Osteoporotic Fractures

*Rola Kwayess, Nada Youssef, ASMA ARABI American University of Beirut, Lebanon

- Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant clonal plasma cell disorder, typically detected incidentally when protein electrophoresis is requested for variable clinical symptoms.
- Although characterized by being clinically asymptomatic and the absence of end organ damage such as lytic lesions, clinical studies showed that MGUS patients may develop vertebral fractures
- this is a retrospective chart review of patients with osteoporotic vertebral fractures, presenting to the endocrinology clinics of the American University of Beirut Medical Center between Nov 2018 and Feb 2020.

**Table of characteristics of the study population**

| | Work up done N=34 | Work up not done N=31 | MGUS N-14 41% | Non- MGUS N=20 |
|---|---|---|---|---|
| Age (years) | 70.7 ±11.5 | 68.4 ±13.4 | 73.1 ± 11.3 | 69 ±11.7 |
| Female | 76.5% | 90.3% | 85.7% | 70% |
| T-Score spine | -2.8 ±0.9 | -2.6 ±1.1 | -2.7 ± 1.1 | -2.9 ±0.8 |
| T-Score hip | -2.1 ±0.97 | -1.88 ±0.73 | -2.3 ± 1.0 | -2.0 ±0.9 |
| TBS | 1.17 ±0.1 | 1.22 ±0.1 | 1.19 ± 0.1 | 1.17 ±0.1 |
| N fractures* | 2 | 2 | 2 | 2.5 |

* median number of fractured vertebrae

# LB - 1107

**Blockade of Immune Checkpoint Proteins Fuels Trabecular Bone Loss and Reduces Bone Toughness** *Lawrence Vecchi, III[1], David Kell[2], Christopher Peek[2], Sasidhar Uppuganti[1], Margaret Durdan[3], Kai Han[3], Jailyn Smith[1], Maria Alejandra Hernandez Diaz[1], Rachael Wolters[2], Ann Hanna[1], Jim Cassat[1], James Moon[3], Javid Moslehi[1], Justin Balko[1], Jeff Nyman[1], Megan Weivoda[3], Rachelle Johnson[1]. [1]Vanderbilt University Medical Center, United States, [2]Vanderbilt University, United States, [3]University of Michigan, United States

Immune checkpoint inhibitors (ICIs) lead to prolonged survival in cancer patients and in some cases complete regression of metastatic disease. ICIs block interactions of immune checkpoint proteins (e.g., PD-1, PD-L1, CTLA-4) with their cognate receptors, allowing T cell activation and killing of tumor cells. Rheumatologic toxicities are widely reported in patients receiving single or multiple ICIs, and patients are at increased risk of vertebral fracture. To date, no pre-clinical studies have rigorously examined whether ICIs induce bone loss. We hypothesized that blockade of immune checkpoint proteins creates an inflammatory bone marrow microenvironment, leading to bone loss and reduced bone strength. To test this, we examined bone mineral density (BMD) by DXA and microarchitecture by μCT in 10-14 month old C57Bl/6 male PD1-/-CTLA4+/- mice. Compared to age- and sex-matched wildtype (WT) controls, PD1-/-CTLA4+/- mice had significantly lower BMD (-10%, $p<0.05$) and trabecular bone volume in the distal femoral metaphysis (-74%, $p<0.0001$) (n=4 mice/group). Mice treated with a PD-L1 inhibitor and chemotherapy had a similar reduction in BMD compared to IgG (-8%, $p<0.05$; n=5/group) or single agent controls. Radiographic analysis revealed a significant increase in osteolytic lesion number and area in PD1-/-CTLA4+/- mice compared to WT mice (4-6-fold, $p<0.001$), suggesting elevated resorption. In support of this, osteoclasts derived from mice treated with a PD-1 inhibitor had greater resorptive activity ex vivo (50%, $p<0.05$; n=3-5 mice/group). At the molecular level, homogenized whole femora from the PD1-/-CTLA4+/- mice and anti-PD-L-1 treated mice had increased Tnfsf11/Tnfrsf11b (1.42-9.5-fold) and Cx3cr1 (2-2.25-fold) mRNA, with increased Type I immune response cytokines IL-12, IL-15, and IFNγ (1.4-183-fold), and IL-17A immune cytokines IL-6 and IL-17 (2.75-11.5-fold) in PD1-/-CTLA4+/- mice. To determine whether this leads to reduced cortical bone strength, we performed a 3-point bending test on femora from the PD1-/-CTLA4+/- and WT mice and found a significant reduction in ultimate force (-27%, $p<0.01$), work-to-failure (-55%, $p<0.01$), and post-yield displacement (-50%, $p<0.05$), indicating reduced bone toughness. Together these data suggest that blockade of immune checkpoint proteins activates prolonged T cell responses to create an inflammatory bone microenvironment that sustains bone resorption, leading to an increased risk of fracture following ICI therapy.

***Disclosures: Lawrence Vecchi, III, None***

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