Disclosures

- Research grants from NHMRC, Amgen, Eli-Lilly and Merck

- Honoraria from Amgen, Eli-Lilly, Gilead

- Advisory Board for Amgen, UCB
Differentiating effects of anti-resorptive and anabolic drugs on bone

New data on old drug - teriparatide

Anti-fracture efficacy of the PTHrP analogue, abaloparatide

Anti-fracture efficacy of the monoclonal antibody to sclerostin, romosozumab

An initiative to redesign RCTs for osteoporosis

Some late-breaking news
The Bone Remodelling Unit

HSC → OB precursor → osteoclast → osteoblasts → MSC → OB precursor

osteocytes
Potential Mechanisms of Anti-Resorptive Drugs

A Normal

B Classic antiresorptives

C Uncoupling antiresorptives

Resorption Viability

Bisphosphonates, denosumab

Odanacatib, saracatinib

**Action of Bisphosphonates on Osteoclasts**

- **Bind to bone mineral**
- **Concentrate at sites of bone resorption**
- **Release and intracellular uptake during resorption**

**Osteoclasts are ‘crippled’, ‘disabled’ or ‘frustrated’** (but do not necessarily ‘die’ by apoptosis)

- **BP = bisphosphonates**
- **Loss of resorptive function (via inhibition of FPPS and prenylation of GTP-ases)**

**Bisphophonate (bone surface)**

**Osteoclast membrane**
Selective Inhibition of the Mevalonate Pathway by Statins and Bisphosphonates Is the Result of Selective Tissue Targeting

- **Osteoclasts**
  - N- bisphosphonates
  - Isoprenylation of proteins
  - Bone resorption inhibited

- **Liver**
  - Statins
  - HMG Co-A
  - Mevalonate
  - Farnesyl-PP
  - Geranylgeranyl-PP
  - Squalene
  - Cholesterol synthesis inhibited

- **Bone resorption inhibited**
- **Cholesterol synthesis inhibited**
Therapeutic Targets in Osteoclast Physiology

Therapeutic Targets in Osteoblast Physiology

Modelling-Directed (A – Anti-Sclerostin Antibodies) versus Remodelling-Directed (B – PTH and abaloparatide) Bone Formation

77% romosozumab
30% teriparatide

70% teriparatide
15% romosozumab

Ke HZ et al., *Endocrine Reviews* 33: 747–783, 2012
Effect of Anti-Sclerostin Antibodies to Increase Bone Formation and Decrease Bone Resorption in Humans
Human Parathyroid Hormone 1-34 [teriparatide] and 1-84


hPTH 1-84
(Crystal structure)$^2$

hPTH (1-34)

hPTH/PTHrP Receptor
Teriparatide in GIOP - 36 Months: Markers of Bone Turnover

***


***p<.001 teriparatide vs. alendronate

Maximum registered lifetime treatment of teriparatide is 18 months.
Teriparatide MOA
Histomorphometry

Dempster D et al., SHOTZ study JBMR July 2016
Teriparatide effects on Trabecular Bone - SHOTZ Study

6 Months
Maximum registered lifetime treatment of teriparatide is 18 months.  

24 Months

1 Dempster D et al., SHOTZ study JBMR July 2016
2 Forteo Australian Product Information, 2 November 2015
Teriparatide Effects on Cortical Bone
SHOTZ Study

6 Months
24 Months

Maximum registered lifetime treatment of teriparatide is 18 months.²

1 Dempster D et al., SHOTZ study JBMR July 2016
2 Forteo Australian Product Information, 2 November 2015
EFFECTS OF 24 MONTHS TREATMENT OF TERIPARATIDE COMPARED WITH RISEDRONATE ON NEW FRACTURES IN POSTMENOPAUSAL WOMEN

KENDLER ET AL., UNIVERSITY OF BRITISH COLUMBIA, CA

- Compare the anti-fracture efficacy of teriparatide (TPTD) with risedronate (RIS) in postmenopausal women with severe osteoporosis (VERO study)

2 year randomized (1:1), double blind, double-dummy trial

1,360 women mean age 72.1 years at least 2 moderate or 1 severe vertebral fractures low bone mass

TPTD
20 µg sc daily

RIS
35 mg oral weekly
## Conclusions

- In postmenopausal women with severe osteoporosis, the risk for new vertebral and clinical fractures was significantly reduced in patients randomized to TPTD compared to RIS.
- There was a trend to fewer NVF in patients on TPTD compared to RIS.
- These results support TPTD as 1st line treatment for women with severe osteoporosis, superior to RIS antiresorptive therapy.

Reproduced from Osteopors Int 2017: 28 (Suppl1) 70 with permission from Springer
30 Years of PTHrP
University of Melbourne, Professor T Jack Martin FRS AO
Abaloparatide

- Abaloparatide is a novel synthetic peptide analogue of PTHrP
- Retains anabolic activity with decreased bone resorption, less calcium-mobilizing potential, and improved room temperature stability compared with teriparatide
- Studies performed in animals have demonstrated marked bone anabolic activity of abaloparatide with complete reversal of bone loss in ovariectomy-induced osteopenic rats and monkeys
Changes in BMD Following 24 Weeks Treatment with Abaloparatide, Teriparatide or Placebo – Phase 2 Study

Leder BZ et al. J Clin Endocrinol Metab 2014

Figure 2. Mean percent change (±SE) in PA spine BMD, femoral neck BMD, and total hip BMD over 24-weeks by treatment group. ABL=abaloparatide, TPTD=teriparatide. *P < .01 vs placebo. **P < .05 vs placebo. & P < .05 vs teriparatide.
Phase 3 Study – Abaloparatide versus Teriparatide & Placebo

**BMD**

- **A** Total hip
- **B** Femoral neck
- **C** Lumbar spine

**Mean (95% CI) Change in Bone Mineral Density, %**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abaloparatide</td>
<td>822</td>
<td>736</td>
<td>651</td>
<td>615</td>
</tr>
<tr>
<td>Placebo</td>
<td>820</td>
<td>762</td>
<td>693</td>
<td>651</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>818</td>
<td>754</td>
<td>705</td>
<td>660</td>
</tr>
</tbody>
</table>

No. of participants evaluated:

<table>
<thead>
<tr>
<th></th>
<th>822</th>
<th>736</th>
<th>651</th>
<th>615</th>
</tr>
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<td>660</td>
</tr>
</tbody>
</table>

Miller PJ et al., JAMA. 2016; 316(7): 722-733
Phase 3 Study – Abaloparatide versus Teriparatide & Placebo
Fractures

Miller PJ et al., JAMA. 2016; 316(7): 722-733
Phase 3 Study – Abaloparatide versus Teriparatide & Placebo
Bone Turnover Markers

Miller PJ et al., JAMA. 2016; 316(7): 722-733
# Safety and Adverse Events

<table>
<thead>
<tr>
<th>Table 3. Safety and Adverse Events&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Abaloparatide (n = 822)</th>
<th>Placebo (n = 820)</th>
<th>Teriparatide (n = 818)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treatment-emergent adverse events</td>
<td>735 (89.4)</td>
<td>718 (87.6)</td>
<td>727 (88.9)</td>
</tr>
<tr>
<td>Serious treatment-emergent adverse events</td>
<td>80 (9.7)</td>
<td>90 (11.0)</td>
<td>82 (10.0)</td>
</tr>
<tr>
<td>Deaths&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (0.4)</td>
<td>5 (0.6)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Adverse events leading to discontinuation</td>
<td>81 (9.9)</td>
<td>50 (6.1)</td>
<td>56 (6.8)</td>
</tr>
<tr>
<td>Discontinuation due to &gt;7.0% BMD decrease&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1/218 (0.5)</td>
<td>12/184 (6.5)</td>
<td>1/160 (0.6)</td>
</tr>
<tr>
<td>Most frequently observed adverse events&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>93 (11.3)</td>
<td>74 (9.0)</td>
<td>102 (12.5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>82 (10.0)</td>
<td>50 (6.1)</td>
<td>60 (7.3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>71 (8.6)</td>
<td>80 (9.8)</td>
<td>70 (8.6)</td>
</tr>
<tr>
<td>Back pain</td>
<td>70 (8.5)</td>
<td>82 (10.0)</td>
<td>59 (7.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>68 (8.3)</td>
<td>25 (3.0)</td>
<td>42 (5.1)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>68 (8.3)</td>
<td>63 (7.7)</td>
<td>73 (8.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>62 (7.5)</td>
<td>49 (6.0)</td>
<td>51 (6.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>59 (7.2)</td>
<td>54 (6.6)</td>
<td>41 (5.0)</td>
</tr>
<tr>
<td>Influenza</td>
<td>52 (6.3)</td>
<td>39 (4.8)</td>
<td>34 (4.2)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>48 (5.8)</td>
<td>66 (8.0)</td>
<td>53 (6.5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>43 (5.2)</td>
<td>38 (4.6)</td>
<td>41 (5.0)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>42 (5.1)</td>
<td>3 (0.4)</td>
<td>13 (1.6)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>40 (4.9)</td>
<td>49 (6.0)</td>
<td>42 (5.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>37 (4.5)</td>
<td>42 (5.1)</td>
<td>34 (4.2)</td>
</tr>
<tr>
<td>Hypercalciemia (prespecified safety end point)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>28/820 (3.4)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>3/817 (0.4)</td>
<td>52/816 (6.4)</td>
</tr>
<tr>
<td>Adverse events of special interest&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension&lt;sup&gt;h&lt;/sup&gt;</td>
<td>140 (17.1)</td>
<td>134 (16.4)</td>
<td>127 (15.5)</td>
</tr>
<tr>
<td>Neoplasms, benign, malignant, and unspecified&lt;sup&gt;i&lt;/sup&gt;</td>
<td>20 (2.4)</td>
<td>29 (3.5)</td>
<td>31 (3.8)</td>
</tr>
<tr>
<td>Fall&lt;sup&gt;j&lt;/sup&gt;</td>
<td>4 (0.5)</td>
<td>2 (0.2)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Drug hypersensitivity&lt;sup&gt;k&lt;/sup&gt;</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Renal impairment&lt;sup,l&lt;/sup&gt;</td>
<td>2 (0.2)</td>
<td>4 (0.5)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Myocardial infarction&lt;sup,m&lt;/sup&gt;</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values are reported as No. (%) unless otherwise indicated. Statistical testing of adverse events was not prespecified in the statistical analysis plan (Supplement 2), with the exception of hypercalciemia.


<sup>c</sup> The denominator indicates the total number of patients who discontinued study participation.

<sup>d</sup> Indicates adverse events that occurred in at least 5% of patients in any single study group.

<sup>e</sup> Hypercalciemia defined as albumin-corrected serum calcium of at least 10.7 mg/dL (≥ 2.67 mmol/L) at any time point, which was a prespecified safety end point and was analyzed using the χ² test. Values are reported as No. with hypercalciemia/No. in study group (%).

<sup>f</sup> For abaloparatide and teriparatide vs placebo, P < .001; for abaloparatide vs teriparatide, P = .006.

<sup>g</sup> Adverse events of special interest were selected based on those related to mechanism of action, drug class effects and/or ongoing review of the study.

<sup>h</sup> Derived from vital sign data as a decrease in systolic blood pressure of at least 20 mm Hg from a supine position to standing or of at least 10 mm Hg in diastolic blood pressure from a supine position to standing in a postdose measurement.

<sup>i</sup> Summarized by system organ class.

<sup>j</sup> Based on patient self-report and assessed by the investigator.

<sup>k</sup> None of the events of drug hypersensitivity were associated with the study drug but were allergic reactions to other drugs provided to the participant.
### Table 2. Fracture Efficacy End Points After 18 Months of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Study Participants With Fracture, No. (%)a</th>
<th>Abaloparatide vs Placebo</th>
<th>Abaloparatide vs Teriparatide</th>
<th>Teriparatide vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abaloparatide (n = 824)</td>
<td>Placebo (n = 821)</td>
<td>Teriparatide (n = 818)</td>
<td>Abaloparatide (95% CI)b</td>
</tr>
<tr>
<td><strong>Primary End Point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New vertebral fracture</td>
<td>4 (0.6)</td>
<td>30 (4.2)</td>
<td>6 (0.8)</td>
<td>-3.64 (-5.42 to -2.10)</td>
</tr>
<tr>
<td><strong>Secondary End Point</strong></td>
<td>18 (2.7)</td>
<td>33 (4.7)</td>
<td>24 (3.3)</td>
<td>-2.01 (-4.02 to -0.00)</td>
</tr>
<tr>
<td>Nonvertebral fracture</td>
<td>10 (1.5)</td>
<td>34 (6.2)</td>
<td>23 (3.1)</td>
<td>-4.73 (-8.07 to -1.40)</td>
</tr>
<tr>
<td><strong>Exploratory End Points</strong></td>
<td>27 (4.0)</td>
<td>49 (8.3)                 35 (4.8)</td>
<td>-4.24 (-7.93 to -0.54)</td>
<td>0.57 (0.35 to 0.91)</td>
</tr>
</tbody>
</table>

**Abbreviations:** HR, hazard ratio; RD, risk difference.

\(a\) The percentage of new vertebral fractures was calculated using the modified intent-to-treat population at 18 months (placebo, n = 711; abaloparatide, n = 690; teriparatide, n = 717). The percentage of nonvertebral, major osteoporotic, and clinical fractures was cumulative Kaplan-Meier estimates using the intent-to-treat population at 19 months (the entire observational period including 18 months of treatment plus 1 month of follow-up).

\(b\) The 95% CI for RD for new vertebral fractures was calculated using the Newcombe method19; 95% CIs for RDs for nonvertebral, major osteoporotic, and clinical fractures were calculated using the normal approximation with difference in Kaplan-Meier estimates and standard error by Greenwood.20

\(c\) Values are reported as HR (95% CI) unless otherwise indicated.

\(d\) P values for new vertebral fractures were derived using the Fisher exact test. P values for nonvertebral, major osteoporotic, and clinical fractures were calculated using the log-rank test.

\(e\) Values comparing abaloparatide vs placebo, abaloparatide vs teriparatide, and teriparatide vs placebo are reported as relative risks (95% CIs) for new vertebral fractures.
Humans with genetic sclerostin deficiency have high bone mass

Sclerosteosis:
- Rare autosomal recessive disease
- Mutations in the SOST gene result in the absence of functional sclerostin
- Results in high bone mass with anecdotal evidence of fracture resistance
- Heterozygous carriers have a milder high bone mass phenotype
- In SOST knockout mice it was confirmed that high bone mass with sclerostin deficiency leads to greater bone strength

Genetically-induced reductions in sclerostin increase bone mass and bone strength, making sclerostin an attractive therapeutic target

Sclerostin inhibition by romosozumab increases bone formation and decreases bone resorption
Response of Spinal, Total Hip and Femoral Neck BMD to 210 mg Monthly Romosozumab

Response of Bone Formation (PINP) and Bone Resorption (β-CTX) Markers to Romosozumab

Phase 2 Extension – 2 Years Romosozumab Followed By One Year Denosumab

McClung MR et al. JBMR SI 2014 A326
Phase 3 Studies of Anti-Sclerostin Antibodies for Treatment of Post-Menopausal Osteoporosis

• **ARCH Study** - Placebo RCT of romosozumab vs. alendronate for 12 mths, followed by open label alendronate for 12 months with primary end-points of clinical and new vertebral fractures over 2 yrs

• **FRAME Study** - Placebo RCT of romosozumab vs. placebo for 12 mths, followed by open label denosumab for 12 months with primary end-points of clinical and new vertebral fractures over 2 yrs
FRAME Study - Trial Regimens and Assessments

7180 Patients were enrolled

Double-Blind Period
- 3591 received placebo subcutaneously every month
- 3589 received romosozumab, 210 mg subcutaneously every month

Open-Label Period
- Received denosumab, 60 mg subcutaneously every 6 mo
- Daily calcium and vitamin D

Radiography of the thoracic and lumbar spine
Dual-energy x-ray absorptiometry
Serum studies of bone-turnover markers

Month

Extension study
Percentage Change from Baseline in Bone Mineral Density and Levels of Bone Turnover Markers

A. Change in Bone Mineral Density at Lumbar Spine

B. Change in Bone Mineral Density at Total Hip

C. Change in Bone Mineral Density at Femoral Neck

D. Change in P1NP Level

E. Change in β-CTX Level

Incidence of New Vertebral, Clinical, and Nonvertebral Fractures.

A. Incidence of New Vertebral Fracture

- Placebo: 0.5% (16/3321), Placebo → Denosumab: 0.6% (21/3325), Romosozumab: 1.8% (59/3322), Romosozumab → Denosumab: 2.5% (84/3327)

- Risk ratio, 0.27 (P<0.001)

B. First Clinical Fracture in Time-to-Event Analysis

C. First Nonvertebral Fracture in Time-to-Event Analysis

No. at Risk
Placebo: 3591, 3316, 3134, 3037, 2955
Romosozumab: 3589, 3317, 3148, 3050, 2968
### Adverse Events

#### Table 2. Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>12 Months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=3576)</td>
<td>Romosozumab (N=3581)</td>
</tr>
<tr>
<td>Adverse event during treatment†</td>
<td>2850 (79.7)</td>
<td>2806 (78.4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>429 (12.0)</td>
<td>467 (13.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>438 (12.2)</td>
<td>459 (12.8)</td>
</tr>
<tr>
<td>Back pain</td>
<td>378 (10.6)</td>
<td>375 (10.5)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>312 (8.7)</td>
<td>344 (9.6)</td>
</tr>
<tr>
<td>Adjudicated serious cardiovascular event‡</td>
<td>41 (1.1)</td>
<td>44 (1.2)</td>
</tr>
<tr>
<td>Death</td>
<td>23 (0.6)</td>
<td>29 (0.8)</td>
</tr>
<tr>
<td>Adjudicated cardiovascular death‡</td>
<td>15 (0.4)</td>
<td>17 (0.5)</td>
</tr>
<tr>
<td>Event leading to discontinuation of trial regimen</td>
<td>94 (2.6)</td>
<td>103 (2.9)</td>
</tr>
<tr>
<td>Event leading to discontinuation of trial participation</td>
<td>50 (1.4)</td>
<td>44 (1.2)</td>
</tr>
<tr>
<td>Event of interest§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Hypersensitivity¶</td>
<td>245 (6.9)</td>
<td>242 (6.8)</td>
</tr>
<tr>
<td>Injection-site reaction¶</td>
<td>104 (2.9)</td>
<td>187 (5.2)</td>
</tr>
<tr>
<td>Hyperostosis</td>
<td>27 (0.8)</td>
<td>19 (0.5)</td>
</tr>
<tr>
<td>Cancer</td>
<td>69 (1.9)</td>
<td>59 (1.6)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>315 (8.8)</td>
<td>281 (7.8)</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw§</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Atypical femoral fracture§</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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* The population for this analysis included all the patients who underwent randomization and received at least one dose of placebo or romosozumab in the 12-month double-blind period. At month 12, patients made the transition to denosumab for the second year of the trial.† The events listed are the most frequent adverse events in the double-blind period that occurred in 10% or more of the patients in either group.‡ The events listed include adverse events that were adjudicated as positive by an independent adjudication committee. Cardiovascular deaths include fatal events that were adjudicated as being cardiovascular-related or undetermined (presumed to be cardiac-related).§ Events of interest were those that were identified by prespecified Medical Dictionary for Regulatory Activities search strategies.¶ Seven patients in the romosozumab group had serious adverse events during the 12-month double-blind period. Events that were reported by the investigator as being related to romosozumab included dermatitis, allergic dermatitis, and macular rash, all of which resolved; the drug was withdrawn or withheld in these cases.|| The most frequent adverse events of injection-site reactions (occurring in >0.1% of the patients) in the romosozumab group during the 12-month double-blind period included injection-site pain (in 1.7% of the patients), erythema (1.5%), bruising (0.8%), pruritus (0.7%), swelling (0.4%), hemorrhage (0.4%), rash (0.3%), and hematoma (0.2%).
Addressing the Crisis in the Treatment of Osteoporosis: A Path Forward

Sundeep Khosla,¹ Jane A Cauley,² Juliet Compston,³ Douglas P Kiel,⁴ Clifford Rosen,⁵ Kenneth G Saag,⁶ and Elizabeth Shane⁷

¹Robert and Arlene Kogod Center on Aging and Endocrine Research Unit, Mayo Clinic College of Medicine, Rochester, MN, USA
²Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA
³Department of Medicine, Cambridge Biomedical Campus, Cambridge, UK
⁴Institute for Aging Research, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
⁵Maine Medical Research Institute, Portland, ME, USA
⁶University of Alabama at Birmingham, Birmingham, AL, USA
⁷Division of Endocrinology, Department of Medicine, Columbia University, New York, NY, USA
Addressing the Current Crisis in Osteoporosis Treatment

- New drug development to circumvent AFF
- The Biomarkers Consortium-Bone Quality Project is attempting to qualify a surrogate marker for fracture prediction to be used in clinical trials, obviating the need for multiple large randomized trials with fracture as an endpoint
- If such a surrogate marker is approved for osteoporosis drug development, this will provide a financial incentive to bring new drugs to market
Subcutaneous romosozumab for 12 mths followed by alendronate for 12 mths vs. alendronate for 2 yrs

50% RR reduction in vertebral fractures and 27% RR reduction in clinical fractures at 2 yrs (*both* primary study end-points)

19% reduction in non-vertebral fractures at 2 yrs (key secondary end-point)

Nominally significant reduction in hip fractures at 2 yrs

Positively adjudicated cardiovascular serious adverse events were 2.5% (romosozumab) vs 1.9% (ALN) - NNH 167
Thank You!