Disclosures

- **Grants/Research Support from:**
  - Amgen, Eli Lilly

- **Consultant for:**
  - Amgen, Eli Lilly, INESSS, INSPQ, Merck, Osteoporosis Canada, PHAC

- **Speaker’s Bureau for:**
  - Amgen, Eli Lilly
Objectives

1. Summarize the long-term efficacy data with different osteoporosis therapies;
2. Describe the long-term safety data with different osteoporosis therapies;
3. Identify who should have a drug holiday and for how long.
**First Line Therapies with Evidence for Fracture Prevention in Postmenopausal Women***

<table>
<thead>
<tr>
<th>Type of Fracture</th>
<th>Bisphosphonates</th>
<th>Antiresorptive therapy</th>
<th>Bone formation therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vertebral</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td></td>
<td>✓</td>
<td>✓</td>
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<tr>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Hip</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Non-vertebral</strong>*</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

* For postmenopausal women, indicates first line therapies and Grade A recommendation.
For men requiring treatment, alendronate, risedronate, denosumab and zoledronic acid can be used as first line therapies for prevention of fractures [Grade D].
In clinical trials, non-vertebral fractures are a composite endpoint including hip, femur, pelvis, tibia, humerus, radius, and clavicle.
** Hormone therapy (estrogen) can be used as first line therapy in women with menopausal symptoms.
Comparative Effectiveness of Osteoporosis Therapies to Prevent Fragility Fractures: A Systematic Review and Meta-Analysis

Background

- An Endocrine Society meta-analysis undertaken at the Mayo clinic
- Meta-analysis of randomized controlled trials evaluating the efficacy of bisphosphonates, denosumab, teriparatide, selective estrogen receptor modulators, or calcium and vitamin D
- It is a meta-analysis of 116 trials
  - n=139,647 patients, median age 64 years

### Meta-analysis of Efficacy of Osteoporosis Therapies: Vertebral Fracture

<table>
<thead>
<tr>
<th>First Line</th>
<th>Odds ratio</th>
<th>CI</th>
<th>P-Value</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teriparatide</td>
<td>0.30</td>
<td>0.16 - 0.55</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td>0.33</td>
<td>0.19 - 0.65</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>0.35</td>
<td>0.20 - 0.64</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Risedronate</td>
<td>0.46</td>
<td>0.31 - 0.68</td>
<td>0.00</td>
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</tr>
<tr>
<td>Alendronate</td>
<td>0.50</td>
<td>0.33 - 0.79</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>0.57</td>
<td>0.39 - 0.83</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Bazedoxifene</td>
<td>0.61</td>
<td>0.32 - 1.18</td>
<td>0.14</td>
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</tr>
<tr>
<td>Ibandronate</td>
<td>0.62</td>
<td>0.37 - 0.98</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>0.71</td>
<td>0.45 - 1.12</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>0.96</td>
<td>0.59 - 1.58</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>VitD+Calcium</td>
<td>0.99</td>
<td>0.74 - 1.41</td>
<td>0.95</td>
<td></td>
</tr>
</tbody>
</table>

Odds Ratio (OR) < 1 Favors treatment
OR > 1 Favors control

## Meta-analysis of Efficacy of Osteoporosis Therapies: Hip Fracture

### First Line

<table>
<thead>
<tr>
<th>First Line</th>
<th>Odds ratio</th>
<th>CI Limits</th>
<th>P-Value</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teriparatide</td>
<td>0.42</td>
<td>0.10</td>
<td>1.82</td>
<td>0.24</td>
</tr>
<tr>
<td>Alendronate</td>
<td>0.45</td>
<td>0.27</td>
<td>0.68</td>
<td>0.00</td>
</tr>
<tr>
<td>Risedronate</td>
<td>0.48</td>
<td>0.31</td>
<td>0.66</td>
<td>0.00</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>0.49</td>
<td>0.20</td>
<td>1.82</td>
<td>0.11</td>
</tr>
<tr>
<td>Denosumab</td>
<td>0.50</td>
<td>0.27</td>
<td>0.86</td>
<td>0.03</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>0.50</td>
<td>0.34</td>
<td>0.73</td>
<td>0.00</td>
</tr>
<tr>
<td>Vit.D+Calcium</td>
<td>0.81</td>
<td>0.68</td>
<td>0.96</td>
<td>0.02</td>
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<tr>
<td>Raloxifene</td>
<td>0.87</td>
<td>0.63</td>
<td>1.22</td>
<td>0.41</td>
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<tr>
<td>Vitamin D</td>
<td>1.13</td>
<td>0.95</td>
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<td>0.18</td>
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<tr>
<td>Calcium</td>
<td>1.14</td>
<td>0.82</td>
<td>1.59</td>
<td>0.44</td>
</tr>
</tbody>
</table>

**Odds Ratio (OR) < 1**: Favors treatment  
**OR > 1**: Favors control

### Meta-analysis of Efficacy of Osteoporosis Therapies: Non-vertebral Fracture

<table>
<thead>
<tr>
<th>First Line</th>
<th>Odds ratio</th>
<th>CI Lower</th>
<th>CI Upper</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teriparatide</td>
<td>0.50</td>
<td>0.32</td>
<td>0.78</td>
<td>0.00</td>
</tr>
<tr>
<td>Risedronate</td>
<td>0.68</td>
<td>0.55</td>
<td>0.81</td>
<td>0.00</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>0.69</td>
<td>0.55</td>
<td>0.84</td>
<td>0.00</td>
</tr>
<tr>
<td>Denosumab</td>
<td>0.74</td>
<td>0.56</td>
<td>0.94</td>
<td>0.03</td>
</tr>
<tr>
<td>Alendronate</td>
<td>0.78</td>
<td>0.66</td>
<td>0.92</td>
<td>0.00</td>
</tr>
<tr>
<td>Bazedoxifene</td>
<td>0.85</td>
<td>0.65</td>
<td>1.11</td>
<td>0.23</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>0.88</td>
<td>0.43</td>
<td>1.64</td>
<td>0.73</td>
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<tr>
<td>Raloxifene</td>
<td>0.90</td>
<td>0.76</td>
<td>1.03</td>
<td>0.22</td>
</tr>
<tr>
<td>VitD+Calcium</td>
<td>0.94</td>
<td>0.84</td>
<td>1.02</td>
<td>0.28</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.00</td>
<td>0.82</td>
<td>1.22</td>
<td>1.00</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>1.01</td>
<td>0.82</td>
<td>1.20</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Odds Ratio (OR) < 1 Favors treatment

OR > 1 Favors control

Reduction in Mortality Risk with Osteoporosis Treatments: Meta-analysis

Osteonecrosis of the jaw (ONJ)
- Very rare (1/100,000 person-years) with bisphosphonates and denosumab in postmenopausal osteoporosis
- Average annual incidence with metastatic cancer doses of denosumab or bisphosphonate (12 to 15 times what is used in osteoporosis) 2 to 5%

Atypical Femur Fracture (AFF)
- Very rare (2-78/100,000 person-years) with bisphosphonates and denosumab in postmenopausal osteoporosis

Severe Hypocalcemia
- Rare occurrence with i.v. zoledronic acid and denosumab, usually in patients with calcium malabsorption, vitamin D insufficiency, secondary hyperparathyroidism, and/or renal insufficiency

Very Rare Potential Harms Associated with Osteoporosis Medications

- **Atrial fibrillation with bisphosphonate**
  - No association with oral bisphosphonates; FDA warning of persistent increased risk of AF with longer use of annual i.v. zoledronic acid

- **Esophageal cancer with oral bisphosphonate**
  - No increased risk

- **Osteosarcoma with teriparatide**
  - Seen in rat after lifelong therapy with high dose teriparatide
  - No excess incidence of osteosarcoma noted with over 1 million treated patients\(^3\)
  - The Osteosarcoma Surveillance Study (OSS) reported 7-year interim analysis which did not detect an association of teriparatide or recombinant human PTH use and incidence of osteosarcoma\(^4\)

Osteoporosis Therapies: Proven Benefits Outweigh Rare Risks

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence per 100,000 person years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bis-ONJ</td>
<td>1.03</td>
</tr>
<tr>
<td>Bis-AFF (8yr)</td>
<td>78</td>
</tr>
<tr>
<td>Bis-AFF (2yr)</td>
<td>2</td>
</tr>
<tr>
<td>Murder</td>
<td>1.62</td>
</tr>
<tr>
<td>Fatal MVA</td>
<td>8.4</td>
</tr>
</tbody>
</table>

Major osteoporotic fracture in low-risk women: 650

Major osteoporotic fracture in moderate-risk women: 1600*

Alendronate treatment in osteoporotic woman without vertebral fracture: ≈ 1700 fractures avoided†

Major osteoporotic fracture in high-risk women: 3100*

Alendronate treatment in osteoporotic women with prior vertebral fracture: ≈ 3300 fractures avoided‡

(Rates for murder are from Stats Can and represent national rates. Rates for MVA fatalities are also national rates.)

If patients at risk of hip fracture are treated with bisphosphonates, 100 typical hip fractures will be prevented for every potential associated AFF.

Bis-ONJ = bisphosphonate-associated osteonecrosis of the jaw; Bis-AFF = bisphosphonate-associated atypical subtrochanteric and diaphyseal femur fracture; MVA = motor vehicle accident; *10-year risk of major osteoporotic fracture by Canadian FRAX.
† About 700 nonvert (blue bar) and 1000 clinical vertebral fractures (red bar) would be avoided. Liberman UA et al. NEJM 1995;333:1437-1443.
‡ About 1000 nonvert (blue bar) and 2300 clinical vertebral fractures (red bar) would be avoided. Black DM et al. Lancet 1996;348:1535-1541.
Issues in Evaluating Long-term Efficacy and Safety in Osteoporosis Fracture Trials

Limiting factors:

- Placebo-controlled RCTs are only 3 years long
- Elderly population with increasing risk of fracture
- Sample size calculated for 3 years not longer

Open-label extension studies (6 to 10 years):

- Main objective: Safety
- Surrogates for efficacy: BMD, BTMs
  Rates of fracture
Total Hip BMD Changes from FIT Baseline (mITT*)

Mean Percent Change (± SE) in Total Hip BMD from Original FIT Baseline

Area with lighter shading is open-label use period

\[ \text{Mean Percent Change} \pm \text{SE} \]

\[ P < 0.001 \ ALN/ALN \ vs \ ALN/PBO \]

\[ \text{Year} \]

\[ \text{Area with lighter shading is open-label use period} \]

\[ \text{\(\Delta\) = ALN/Placebo} \]

\[ \text{\(\square\) = ALN/ALN (Pooled 5 mg and 10 mg groups)} \]


*modified intention-to-treat : participants with at least one follow-up point after FLEX baseline
Urinary NTx Changes from FIT Baseline (PP*)

Mean Percent Change (± SE) of Urinary NTx from Original FIT Baseline

Area with lighter shading is open-label use period

- ▲ = ALN/Placebo
- ■ = ALN/ALN (Pooled 5 mg and 10 mg groups)

Year

*per-protocol: participants adherent to treatment

P<0.001 ALN/ALN vs ALN/PBO
In FLEX only, from month 0 to month 120

Effect of Long-term Alendronate Treatment on Clinical Fracture Risk

**Clinical Vertebral Fracture Risk**

FLEX treatment group:*

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Placebo</th>
<th>Alendronate (pooled)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>437</td>
<td>421</td>
</tr>
<tr>
<td>Alendronate</td>
<td>662</td>
<td>642</td>
</tr>
</tbody>
</table>

Cumulative Incidence (%)

- **Cumulative Incidence (%):**
  - Placebo: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20
  - Alendronate (pooled): 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20

**RR, 0.45**

(95% CI, 0.24, 0.86)

**Time to First Fracture (Month):**

0, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72

**Clinical Nonvertebral Fracture Risk**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Placebo</th>
<th>Alendronate (pooled)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>396</td>
<td>373</td>
</tr>
<tr>
<td>Alendronate</td>
<td>585</td>
<td>537</td>
</tr>
</tbody>
</table>

Cumulative Incidence (%)

- **Cumulative Incidence (%):**
  - Placebo: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20
  - Alendronate (pooled): 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20

**RR, 1.00**

(95% CI, 0.76, 1.32)

**Time to First Fracture (Month):**

0, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72

RR = relative risk; *All patients included in FLEX received alendronate in FIT, and results from the alendronate group was pooled from the alendronate 5 mg/day and 10 mg/day groups.

Fracture Risk After Alendronate Discontinuation: FLEX Study

- After discontinuation of alendronate: 22% of women experienced fracture during the subsequent 5 years\(^1\)

- Older age, prevalent fragility fracture, hip BMD < -2.5 strongly predict fracture risk after 5 years of alendronate therapy\(^1\)

- Neither 1-year change in hip BMD nor 1- or 3-year change in bone turnover markers (NTX/ BSAP) predict the risk of fracture after discontinuation\(^2\)

6 Years of ZOL Treatment Maintains Increases in FN BMD

Core Study Population

- Placebo
- Z3

Change From Baseline in FN BMD (%)

-3.0  -2.0  -1.0  0.0  1.0  2.0  3.0  4.0  5.0

Years:

0 0.5 1.0 1.5 2.0 2.5 3.0

Core study

Placebo vs Z3:

5.06%*

Start of extension trial

Subset of Core Study Population

- Z6
- Z3P3

Change From Baseline in FN BMD (%)

-3.0  -2.0  -1.0  0.0  1.0  2.0  3.0  4.0  5.0  6.0

Years:

0 1.0 2.0 3.0 4.0 5.0 6.0

Core + Extension study

Placebo vs Z6 vs Z3P3:

1.4% (0.58, 2.15) P < 0.0001**

0.75% (0.02, 1.48) P=0.0444

+4.5%

0.47% NS (-0.15, 1.10)

+3.1%

-0.06% NS (-0.38, 0.77)

-0.12% NS (-0.57, 0.45)

Change From Baseline in FN BMD (%)

Core study:

Z3 n= 3851
PBO n= 3845

Z6 n= 589 609 608 600 524 450
Z3P3 n= 599 613 606 602 540 467

*P < 0.0001, P value computed from 3-way ANOVA with treatment, stratum and region as explanatory variables

**P value computed from 2-way ANOVA with treatment and region as explanatory variables.

MITT = modified intention to treat

6 Years of ZOL Treatment Maintains Reduction in $\beta$-CTX (ITT)

- Mean values remained within the premenopausal reference range throughout.

$\bullet$ \* $P < 0.05$. No significant difference at any other time point in the extension study. Horizontal dashed lines represent premenopausal reference range (Adapted from Black DM, et al. *N Engl J Med*. 2007;356:1809-1822). ITT = intention to treat, Z3P3 = ZOL for 3 years and placebo for 3 years, Z6 = ZOL for 6 years.
Significantly Fewer New Morphometric Vertebral Fractures in Years 3-6 (Z6 vs Z3P3)

Core study:†P < 0.001 relative risk reduction vs placebo (PBO)

*P = 0.0348, relative risk reduction vs Z3P3; n = the number of patients in the analysis population with X-rays at Year 3 and Year 6

ITT = intention to treat, Z3P3 = ZOL for 3 years and placebo for 3 years, Z6 = ZOL for 6 years

Similar Risk of Nonvertebral Fracture in Years 3–6 (Z6 vs Z3P3)

- **Core study**: 10.7% (388/3875) vs 8% (292/3861)
  - Relative hazard (RH) = 0.99 (0.66, 1.50)
- **Extension study**: 7.6%† (45/616) vs 8.2%† (47/617)

*P < 0.001; †The event rate is from Kaplan-Meier estimate at Month 36 in the extension study

Key Inclusion Criteria for the Extension:
• Completed the FREEDOM study (completed the 3-year visit, did not discontinue investigational product, and did not miss > 1 dose)
• Not receiving any other osteoporosis medications
Effects of Denosumab Treatment on Bone Turnover Markers Through 10 Years

Unpublished data
Effects of Denosumab Treatment on Lumbar Spine BMD and New Vertebral Fractures Through 10 Years

Unpublished data
Effects of Denosumab Treatment on Total Hip BMD and Nonvertebral Fractures Through 10 Years

Unpublished data
Exposure-adjusted Subject Incidence of Adverse Events (Rates per 100 Subject-years)

Unpublished data
Summary

• Denosumab treatment for up to 10 years was associated with:
  – persistent reduction of bone turnover
  – continued increases in BMD without therapeutic plateau
  – low incidence of new vertebral and nonvertebral (including hip) fracture

• The benefit/risk profile for denosumab in an aging population of postmenopausal women remains favorable
Yearly Nonvertebral Fracture Incidence With Denosumab Treatment for Up to 7 Years

- **Long-term DMAB Treatment**
  - Yearly Incidence of Nonvertebral Fractures (%)
  - Years of DMAB Treatment: 1 (2.0%), 2 (1.8%), 3 (2.0%)
  - n: 46, N: 2343

- **Cross-over DMAB Treatment**
  - Yearly Incidence of Nonvertebral Fractures (%)
  - Years of DMAB Treatment: 1 (2.5%), 2 (1.9%), 3 (2.2%)
  - n: 53, N: 2207

n = number of subjects who had ≥ 1 nonvertebral fracture. Percentages for nonvertebral fractures are Kaplan-Meier estimates.
Nonvertebral Fracture Rate Ratios: All Denosumab-treated Subjects

Rate Ratio (95% CI) = 0.62 (0.46–0.83)  
\( P = 0.002 \)

Fracture Rate per 100 Subject-years (95% CI)

- First 3 Years: 2.08
- 4th Year: 1.27

Fractures \( n = 254 \), DMAP Treatment \( n = 50 \), \( N = 4073 \)

\( N \) = number of subjects who did not miss >1 dose of DMAP during the first 3 years of FREEDOM or the extension.

Duration of Therapy/Drug Holiday
Approach to the Management of Postmenopausal Women on Long-term Bisphosphonate Therapy

Post-menopausal women treated with oral (≥ 5yrs) or IV (≥ 3 yrs) BPs

Hip, spine or multiple other osteoporotic fractures before or during therapy

Yes

Reassess benefits/risks
Consider continue BP (1) or change to alternative therapy (2)
Reassess every 2-3 years

No

Hip BMD T-Score ≤ -2.5 (3)
OR
High fracture risk (4)

Yes

Reassess benefits/risks
Consider continue BP for up to 10 yrs (1)
or change to alternative therapy (2)
Reassess every 2-3 years

No

Consider drug holiday
Reassess every 2-3 years (5)
Drug Holiday (Bisphosphonate therapy interruption)

1. **Drug holiday** (not retirement) is feasible with ALN, RIS and ZOL after 3-5 years **if patient at moderate risk**
   - If bisphosphonate interrupted, reassess risk (BMD) after
     - 1 yr for risedronate
     - 2 yrs for alendronate
     - 3 yrs for zoledronic acid

2. Long term adverse effects of osteoporosis therapies are offset in high risk patients by the benefits of long-term reduction in fractures

No Drug Holiday For Reversible Drugs

- Hormone therapy (HT)
- Selective estrogen receptor Modulators (SERM)
- Denosumab
- Teriparatide

Reversibility of Denosumab Action on Bone Turnover and Bone Mineral Density

Includes subjects who enrolled in the off-treatment phase; Reference: 1Bone J Clin Endocrinol Metab 2011

BMD: bone mineral density; CI: confidence interval; CTX: carboxy-terminal collagen crosslinks; P1NP: amino-terminal propeptide of type I collagen; Q1, Q3: first, third quartile
Summary and Conclusion

• Osteoporosis is a chronic disease requiring prolonged treatment.

• Long-term efficacy and safety data for osteoporosis therapies are reassuring

• High risk patients: hip, spine or multiple fragility fractures before or during treatment should continue on BPs up to 10 yrs or consider alternative therapy

• Drug holiday is feasible with ALN, RIS and ZOL after 3-5 years if patient at moderate risk

• No drug holiday for reversible drugs: HT, SERMs, DMAb, TPTD