Effect of Abaloparatide on Bone Mineral Density and Fracture Incidence in Postmenopausal Women with Osteoporosis and Type 2 Diabetes Mellitus

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Disclosures

- R Dhaliwal: participated on a scientific advisory board for Ultragenyx
- D Hans: co-owner of the trabecular bone score (TBS) patent, is a part-time employee of Medimaps Group, and owns company stock
- G Hattersley, B Mitlak, Y Wang, and L Fitzpatrick: employees of and shareholders in Radius Health, Inc.
- A Schwartz: participated in a scientific advisory board for Amgen and has received a research grant from Hologic
- PD Miller: consultant to Radius Health, Inc.; has participated on scientific advisory boards for AgNovos, Alexion, Amgen, El Lilly, Merck, Radius Health, Inc., Roche, and Sanofi; has received research grants from Alexion, Amgen, Boehringer Ingelheim, Immunodiagnostics, El Lilly, Merck, Merck Serrano, National Bone Health Alliance, Novartis, Novo Nordisk, Roche Diagnostics, and Takeda
- R Josse: has participated in scientific advisory boards for Amgen, NovoNordisk, Janssen, El Lilly, and Astra Zeneca; and has received speaker honoraria from Amgen and Novo Nordisk

Introduction: Osteoporosis and Diabetes

- Osteoporosis and diabetes are often comorbid conditions
- Compared with the general population, patients with type 2 diabetes mellitus (T2DM)
  - Have approximately twice the risk of hip fractures
  - Often exhibit higher bone mineral density (BMD)
- In T2DM, bone fragility is a result of deterioration in bone quality
- Arterial BMD (aBMD) measurements, commonly used in the diagnosis of osteoporosis and assessment of fracture risk, are often insensitive to changes in bone quality
- Trabecular bone score (TBS) is strongly correlated with microarchitectural parameters that reflect bone strength and is lower in patients with T2DM compared with the general population
- TBS may improve fracture risk assessment in patients with T2DM in conjunction with aBMD

Introduction: Abaloparatide

- Abaloparatide (ABL) is a selective activator of the parathyroid 1 receptor (PTH1R) signaling pathway\(^1\) that favors the stimulation of bone formation

- In preclinical\(^2\) and clinical\(^3\) studies ABL has
  - Increased BMD\(^2\)\(^5\)\(^7\)
  - Improved bone microarchitecture\(^2\)\(^3\)\(^6\)
  - Increased bone strength\(^3\)\(^4\)

\(^{41}\%\) homology to hPTH (1-34) and 76\% homology to hPTHrP (1-24)

ACTIVE (Abaloparatide Comparator Trial In Vertebral Endpoints) was the pivotal phase 3 study for ABL\(^1\)

- 2463 women with postmenopausal osteoporosis (PMO) age 49 to 86 were included in the intent-to-treat population (ITT) population\(^1\)
- ABL significantly increased BMD and decreased the risk of new vertebral, nonvertebral, and clinical fractures and of major osteoporotic fractures (MOF) vs placebo and of MOF vs teriparatide (TPTD)\(^1\)

Objective

- In this post hoc analysis, we evaluate the efficacy of ABL in the subgroup of ACTIVE patients with T2DM

Methods

- Patients with T2DM were identified by review of medical history records
- Incidence of nonvertebral, clinical, major osteoporotic, and wrist fractures were evaluated using the intent-to-treat (ITT) population
- New vertebral fracture incidence was evaluated using the modified ITT (mITT) population, which included all ITT participants who had both pretreatment and postbaseline spine x-rays
- Patients who had their initial BMD measurement on a TBS-compatible dual-energy x-ray absorptiometry scanner were eligible for inclusion in the TBS analysis
- Missing BMD data were imputed using last observation carried forward (LOCF)
- Lumbar spine TBS was evaluated at baseline and Months 6 and 18
- Change in lumbar spine TBS relative to baseline was assessed by generalized estimating equations (GEE; adjusted for baseline TBS, treatment, visit, and treatment and visit interaction) and by percentage change from baseline
Results: ACTIVE Baseline Clinical Characteristics

- 271 patients were included in the ACTIVE T2DM fracture incidence and BMD subgroup analysis

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>PBO (n=88)</th>
<th>ABL (n=93)</th>
<th>TPTD (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>70.0 (60–82)</td>
<td>69.0 (55–83)</td>
<td>69.0 (55–84)</td>
</tr>
<tr>
<td>Mean femoral neck (FN) T-score</td>
<td>–2.22</td>
<td>–2.20</td>
<td>–2.19</td>
</tr>
<tr>
<td>Prevalent vertebral fracture, n (%)</td>
<td>13 (14.8)</td>
<td>15 (16.1)</td>
<td>22 (24.4)</td>
</tr>
<tr>
<td>≥1 prior nonvertebral fracture within 5 years prior to randomization, n (%)</td>
<td>21 (23.9)</td>
<td>23 (24.7)</td>
<td>26 (28.9)</td>
</tr>
<tr>
<td>No prior fractures, n (%)</td>
<td>40 (45.5)</td>
<td>45 (48.4)</td>
<td>33 (36.7)</td>
</tr>
</tbody>
</table>

ABL, abaloparatide; PBO, placebo; TPTD, teriparatide; T2DM, type 2 diabetes mellitus.

Results: Fracture Incidence for Patients with T2DM

Fracture incidence was lowest in ABL-treated patients and highest in patients treated with PBO. Differences were not statistically significant vs PBO except for nonvertebral fractures (ABL vs PBO, \( P < 0.05 \)).

Results: Change in Total Hip BMD Relative to Baseline for Patients with T2DM

At 6, 12, and 18 months, significant total hip BMD increases \( (P<0.001) \) were observed for ABL vs PBO. No interactions between T2DM status and the treatment effect of ABL on fractures, or BMD increases were observed. BMD and fracture results were similar for TPTD vs PBO.
Results: Change in Femoral Neck BMD Relative to Baseline for Patients with T2DM

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Month</th>
<th>% Change from Baseline (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL (n=93)</td>
<td>0</td>
<td>-2.0 (-2.5 to -1.4)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>-4.0 (-4.6 to -3.4)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>-6.0 (-6.6 to -5.4)</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>-8.0 (-8.6 to -7.4)</td>
</tr>
<tr>
<td>TPTD (n=65)</td>
<td>0</td>
<td>-2.1 (-2.6 to -1.6)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>-4.3 (-4.8 to -3.8)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>-6.4 (-7.0 to -5.8)</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>-8.6 (-9.2 to -8.0)</td>
</tr>
<tr>
<td>PBO (n=68)</td>
<td>0</td>
<td>-2.2 (-2.7 to -1.7)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>-4.5 (-5.0 to -4.0)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>-6.7 (-7.3 to -6.1)</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>-8.9 (-9.5 to -8.3)</td>
</tr>
</tbody>
</table>

At 12 and 18 months, significant femoral neck BMD increases (P<0.001) were observed for ABL vs PBO. No interactions between T2DM status and the treatment effect of ABL on fractures, or BMD increased were observed. BMD and interaction results were similar for TPTD vs PBO.

Results: Change in Lumbar Spine BMD Relative to Baseline for Patients with T2DM

<table>
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<tr>
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<th>Month</th>
<th>% Change from Baseline (95% CI)</th>
</tr>
</thead>
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<tr>
<td>ABL (n=93)</td>
<td>0</td>
<td>-2.0 (-2.5 to -1.4)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>-4.0 (-4.6 to -3.4)</td>
</tr>
<tr>
<td></td>
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<td>-6.0 (-6.6 to -5.4)</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>-8.0 (-8.6 to -7.4)</td>
</tr>
<tr>
<td>TPTD (n=65)</td>
<td>0</td>
<td>-2.1 (-2.6 to -1.6)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>-4.3 (-4.8 to -3.8)</td>
</tr>
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<td>-6.4 (-7.0 to -5.8)</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>-8.6 (-9.2 to -8.0)</td>
</tr>
<tr>
<td>PBO (n=68)</td>
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</tr>
<tr>
<td></td>
<td>6</td>
<td>-4.5 (-5.0 to -4.0)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>-6.7 (-7.3 to -6.1)</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>-8.9 (-9.5 to -8.3)</td>
</tr>
</tbody>
</table>

At 6, 12, and 18 months, significant lumbar spine BMD increases (P<0.001) were observed for ABL vs PBO. No interactions between T2DM status and the treatment effect of ABL on fractures, or BMD increases were observed. BMD and interaction results were similar for TPTD vs PBO.

Results: Change in Lumbar Spine TBS Relative to Baseline for Patients with T2DM

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Month</th>
<th>% Change from Baseline (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL (n=85)</td>
<td>0</td>
<td>-2.0 (-2.5 to -1.4)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>-4.0 (-4.6 to -3.4)</td>
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<tr>
<td></td>
<td>12</td>
<td>-6.0 (-6.6 to -5.4)</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>-8.0 (-8.6 to -7.4)</td>
</tr>
<tr>
<td>TPTD (n=87)</td>
<td>0</td>
<td>-2.1 (-2.6 to -1.6)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>-4.3 (-4.8 to -3.8)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>-6.4 (-7.0 to -5.8)</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>-8.6 (-9.2 to -8.0)</td>
</tr>
<tr>
<td>PBO (n=79)</td>
<td>0</td>
<td>-2.2 (-2.7 to -1.7)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>-4.5 (-5.0 to -4.0)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>-6.7 (-7.3 to -6.1)</td>
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<thead>
<tr>
<th>Treatment</th>
<th>Month</th>
<th>% Change from Baseline (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL (n=75)</td>
<td>0</td>
<td>-2.0 (-2.5 to -1.4)</td>
</tr>
<tr>
<td></td>
<td>6</td>
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<td>-6.0 (-6.6 to -5.4)</td>
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<td>18</td>
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</tr>
</tbody>
</table>

Both ABL- and TPTD-treated patients had a significant TBS increase vs PBO at 6 and 18 months. TBS changes for ABL were numerically larger than TPTD at 6 and 18 months although the differences were not statistically significant.
Conclusion

- In women with PMO and comorbid T2DM, compared with PBO, ABL treatment resulted in
  - Numerical reduction for all fracture types studied along with significant improvements in BMD consistent with the overall ACTIVE population\(^1\)
  - Significant improvement in lumbar spine TBS, suggesting that ABL improved bone microarchitecture


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ACTIVE study sites countries

Q & A