Indications to teriparatide treatment in patients with osteoporosis

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A position paper on the situation in Switzerland

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Summary

To prevent osteoporotic fracture occurrence, a variety of treatment regimens with different mechanisms of action is available. The antiresorptive bisphosphonate drugs are currently the most commonly prescribed agents in the management of patients with osteoporosis. The recombinant amino-terminal fragment of human parathyroid hormone (Teriparatide) is a bone anabolic agent which reduces fracture risk by increasing bone mass and improving bone microarchitecture. Teriparatide treatment reduces vertebral and non-vertebral fracture risk markedly in women and men with idiopathic osteoporosis, or with glucocorticoid-induced osteoporosis. Teriparatide should thus be considered as first line treatment for postmenopausal women and for men with severe osteoporosis.

Key words: osteoporosis; fracture; risk; treatment; glucocorticoids; bisphosphonates

Introduction

Teriparatide (Forsteo®) is a recombinant formulation of endogenous parathyroid hormone (PTH), containing a 34-amino-acid sequence which is identical to the N-terminal portion of the human hormone [rhPTH(1-34)]. It has been shown to increase bone mineral density, and to reduce both vertebral and non-vertebral fracture risk in a phase III pivotal randomised trial which lasted for a mean period of 19 months [17]. The tolerance and safety were considered as excellent. The bone structural changes under therapy are in favour of higher strength. Indeed, teriparatide treatment has been shown to increase trabecular thickness and connectivity, as assessed by microcomputed tomography of iliac crest bone biopsy specimens [47]. In addition, the efficacy of teriparatide in increasing BMD was also demonstrated in patients under glucocorticoid therapy [22, 23]. In a head-to-head trial, it was shown to be even superior to alendronate in terms of BMD changes. Though the trial, which lasted 3 years, was not designed to demonstrate a superiority for fracture risk reduction, it turned out that patients with GIOP receiving teriparatide had fewer vertebral fractures than those in the alendronate group.

In Switzerland teriparatide is approved for the treatment of postmenopausal women with osteoporosis and increased fracture risk, for the treatment of primary or hypogonadism-induced osteoporosis in men, with increased fracture risk, and for the treatment of adults with glucocorticoid-induced osteoporosis (GIOP) and increased fracture risk.

Currently, the reimbursement of teriparatide in Switzerland is limited to a second-line treatment of postmenopausal women and of men, with an x-ray examination detecting new osteoporotic vertebral fracture after a treatment with calcitonine, SERM (selective estrogen receptor modulator), denosumab or bisphosphonates for at least 6 months. In men and women with established GIOP, its use is restricted to cases with a lack of efficacy or intolerance to previous bisphosphonate therapy. The maximum accepted treatment duration is 24 months. Therefore, patients with multiple fracture and low bone mineral density, hence at a very high risk of subsequent fracture, can unfortunately not benefit from this bone anabolic agent as a first line therapy. In the surrounding countries, prescription policy includes women and men with 2 vertebral fractures (France), women and men at increased risk of fracture (Germany), or progression of osteoporosis with vertebral fracture despite antiresorptive therapy for 2 years (Austria).

In March 2011, a panel of Swiss internists, endocrinologists and rheumatologists specialised in the treatment of osteoporosis met to establish a consensus on the treatment in-
dications of teriparatide in osteoprotic women and men. Prior to the meeting, a search of the literature was conducted using online databases. The search was limited to relevant literature on bone mineral density (BMD) and fracture history as predictors of future fractures (vertebral and non-vertebral), in publications addressing evidence on the need for anabolic treatment in patients with severe osteoporosis and in publications focusing on the question of sequential or combination therapy of teriparatide with bisphosphonates or other antiresorptive agents. The panel presented an overview of the current evidence supporting the use of teriparatide in the treatment of osteoporosis, independent of the limitation, and reached a consensus on how the current limitations should be adapted to meet this evidence and fit the needs of the suffering osteoporotic patients.

**Results**

Evidence of bone mineral density and fracture history as predictors of future fractures

In a meta-analysis on prospective cohort studies published between 1985 and the end of 1994 with a baseline measurement of bone density in women and subsequent follow up for fractures, 11 separate study populations with about 90,000 person-year of observation time and over 2000 fractures were identified [1]. All measured anatomic sites had similar predictive abilities for decrease in bone mineral density except for measurement at the spine for predicting vertebral fractures and measurement at the hip for predicting hip fractures which displayed a higher increase of relative risk for each standard deviation decrease in BMD. Another meta-analysis (9,891 men, 29,082 women) showed that BMD measurement at the femoral neck with DXA was a strong predictor of hip fractures, both in men and women [2].

For any given T-score the risk is higher with increasing age [3]. At any age low BMD similarly predicted fracture in men and women. The pattern of 10-year probability with age varied according to fracture type. A study conducted in Switzerland also found that fracture probability increased with age and decreasing BMD T-score [4]. Risk also increased with lower body mass index (BMI) and clinical risk factors used alone or in combination. An additional study determined remaining lifetime and absolute 10-year probabilities for osteoporotic fractures by gender, age, and BMD values [5]. The absolute 10-year probability of osteoporotic fracture increased with advancing age and decreasing BMD and was higher in women than in men. A longitudinal cohort study with a long term follow up of 15 years showed that the absolute risk of an incident morphi-
metric vertebral fracture increased with decreasing BMD measured at the total hip, the femoral neck, and the lumbar spine [7].

Regarding the influence of prevalent fractures on the risk for future fractures, it seems that more than half of the women with five or more fractures at baseline developed new vertebral fractures, compared to only 3.8% of women without prior vertebral fractures. The presence of one or more vertebral fractures at baseline increased the risk of sustaining a new vertebral fracture by 5-fold during the initial year of the study compared with the incidence in subjects without prevalent vertebral fractures at baseline (RR 5.1; 95% CI 3.1–8.4; P <0.001) [9]. The risk of vertebral fracture was greatest among women with a prevalent vertebral fracture at baseline, irrespective of their BMD. The absolute risk of vertebral fractures was more than 50% among women with both a prevalent vertebral fracture and BMD in the osteoporotic range.

In addition, baseline vertebral fracture severity was shown to be predictive for new vertebral (and non-vertebral) fracture risk [10]. Baseline severity of prevalent vertebral fractures was the only predictor of non-vertebral fracture risk and remained a significant predictor even after adjustment for baseline characteristics, including baseline BMD [10]. Similar observations were reported by Roux et al. in 2007 [11].

A systematic review on the role of prevalent fracture for the risk of subsequent fracture [12], showed that women with pre-existing vertebral fractures (identified at baseline by vertebral morphometry) had approximately 4 times greater risk of subsequent vertebral fractures than those without prior fractures. Similar data were reported by Kanis et al. [13]. This risk increased with the number of prior vertebral fractures (table 1).

Table 1: Risk ratio for fracture according to the number of prior morphometric vertebral fractures.

<table>
<thead>
<tr>
<th>Outcome fracture</th>
<th>Number of fractures</th>
<th>Sex</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black [31]</td>
<td>Vertebral</td>
<td>F</td>
<td>1.0</td>
<td>3.2</td>
<td>5.4</td>
<td>10.6</td>
</tr>
<tr>
<td>Lunt [32]</td>
<td>Vertebral</td>
<td>M+F</td>
<td>1.0</td>
<td>3.2</td>
<td>9.8</td>
<td>23.3</td>
</tr>
<tr>
<td>Delmas [10]</td>
<td>Vertebral</td>
<td>F</td>
<td>1.0</td>
<td>3.1</td>
<td>4.4</td>
<td>8.4</td>
</tr>
<tr>
<td>Siris [33]</td>
<td>Vertebral</td>
<td>F</td>
<td>1.0</td>
<td>3.1</td>
<td>5.5</td>
<td>8.6</td>
</tr>
<tr>
<td>Puisto [34]</td>
<td>Hip</td>
<td>M+F</td>
<td>1.0</td>
<td>1.2</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
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<td>1.6</td>
<td>1.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Black [31]</td>
<td>Hip</td>
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<td>1.0</td>
<td>2.0</td>
<td>2.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Delmas [10]</td>
<td>Non-vertebral</td>
<td>F</td>
<td>1.0</td>
<td>1.3*</td>
<td>1.8*</td>
<td>1.4*</td>
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<tr>
<td>Black [31]</td>
<td>Forearm</td>
<td>F</td>
<td>1.0</td>
<td>1.4</td>
<td>1.5</td>
<td>1.4*</td>
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</table>

<table>
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<tr>
<th>Number of prior fractures</th>
<th>Sex</th>
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<th>1</th>
<th>2</th>
<th>3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black [31]</td>
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<td>1.0</td>
<td>3.2</td>
<td>5.4</td>
<td>10.6</td>
</tr>
<tr>
<td>Lunt [32]</td>
<td>M+F</td>
<td>1.0</td>
<td>3.2</td>
<td>9.8</td>
<td>23.3</td>
</tr>
<tr>
<td>Delmas [10]</td>
<td>F</td>
<td>1.0</td>
<td>3.1</td>
<td>4.4</td>
<td>8.4</td>
</tr>
<tr>
<td>Siris [33]</td>
<td>F</td>
<td>1.0</td>
<td>3.1</td>
<td>5.5</td>
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</tr>
<tr>
<td>Puisto [34]</td>
<td>M+F</td>
<td>1.0</td>
<td>1.2</td>
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<td>F</td>
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<td>1.6</td>
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<tr>
<td>Black [31]</td>
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<td>1.0</td>
<td>2.0</td>
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<tr>
<td>Delmas [10]</td>
<td>F</td>
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<td>1.3*</td>
<td>1.8*</td>
<td>1.4*</td>
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<tr>
<td>Black [31]</td>
<td>F</td>
<td>1.0</td>
<td>1.4</td>
<td>1.5</td>
<td>1.4*</td>
</tr>
</tbody>
</table>

History of any fracture during adulthood is a predictor of vertebral and non-vertebral fracture risk. In conclusion, the risk of fragility fractures markedly increases with decreasing BMD, with increasing number of prevalent fractures and with the severity of vertebral fractures.

**Evidence for the need of anabolic treatment in severe osteoporotic patients**

A series of well conducted trials with fracture incidence as endpoint, has demonstrated the antifracture efficacy of antiresorptive treatments such as bisphosphonates, SERMs, Denosumab and hormone replacement therapy. Similar fracture risk reductions were obtained with strontium ranelate [13–15]. The effects of a bone anabolic agent like teriparatide was evaluated in the Fracture Prevention Trial (FPT) which recruited postmenopausal women (mean age 69 ± 7 years) with osteoporosis, with a mean T-score of −2.6 SD and 2.3 ± 1.8 prevalent vertebral fractures. They were treated with teriparatide (20 or 40 µg) [17]. During a mean 19 months duration of the trial, 20 µg and 40 µg doses of teriparatide reduced the risk of one or more new vertebral fractures by 65 and 69 percent, respectively, as compared with placebo. The risk of two or more fractures was reduced by 77 and 86 percent, respectively, and the risk of at least one moderate or severe vertebral fracture was reduced by 90 and 78 percent, respectively. The risk for new non-vertebral fragility fractures was reduced as well by 54%. For comparison, the absolute risk reduction recorded in the various trials with antiresorptives and teriparatide over a similar time period, i.e., 19 months to 2 years are summarised in table 2. In contrast the highly significant reduction of non-vertebral fracture risk with teriparatide in 19 months of treatment, such a reduction does not reach a level of significance for most other agents after 2 years.

Eighteen months after discontinuation of teriparatide treatment, the reduction in fracture risk associated with previous treatment with teriparatide, 20 and 40 µg, was 41% (p = 0.004) and 45% (p = 0.001), respectively, vs. placebo [18]. In addition, Prince et al documented that 30 months after teriparatide discontinuation the risk for new non-vertebral fragility fractures was reduced significantly (Hazard Ratio...
0.62, 95% CI 0.41–0.93; p = 0.022) [19]. Furthermore, it has been demonstrated that teriparatide-treated patients had a reduced incidence of back pain versus those receiving a comparator during an interval including the clinical trials plus 30 months of post-treatment follow-up [20].

Glucocorticoids impair the replication, differentiation and function of osteoblasts and induce the apoptosis of mature osteoblasts and osteocytes [21]. These effects lead to a suppression of bone formation which is a landmark of Glucocorticoid-induced osteoporosis (GIOP). In patients with GIOP, after 18 months of teriparatide treatment there was a significant increase in mean lumbar spine BMD and mean hip BMD vs. alendronate [22]. The incidence of new vertebral fractures was lower in the teriparatide group compared to alendronate. After 36 months, increases in BMD from baseline were significantly greater in the teriparatide group than in the alendronate group (p < 0.001) (fig. 1A B). The final analysis of the fracture incidence showed that fewer subjects had vertebral fractures in the teriparatide group than in the alendronate group (3 [1.7%] of 173 versus 13 [7.7%] of 169; p = 0.007), with most occurring during the first 18 months [22].

Teriparatide has a high efficacy in women with severe osteoporosis (based on T-score) and at least 2 vertebral fractures. Ancillary benefits are that the efficacy of teriparatide in fracture risk reduction persists after discontinuation (vertebral and non-vertebral fractures) and that, during and after treatment, back pain decreases. Furthermore, considering the pathogenesis of GIOP, teriparatide is a well suited treatment for GIOP as its effects on bone formation counteract those of the glucocorticoids.

The issue of cost-effectiveness has been addressed. The cost per QALY gained by a treatment with teriparatide in a population of 69-years-old with a T-score at the femoral neck of -2.5 or lower was always lower than EUR 60,000 [46].

>60 years old with a T-score at the femoral neck of –2.5 or lower was estimated to be between EUR (euro) 20,000 and 64,000 for patients with a neck of -3 and lower was in the base case estimated to be a cost per QALY gained by a treatment with teriparatide in fracture risk reduction persists after discontinuation (vertebral and non-vertebral fractures) and that, during and after treatment, back pain decreases. Furthermore, considering the pathogenesis of GIOP, teriparatide is a well suited treatment for GIOP as its effects on bone formation counteract those of the glucocorticoids.

Table 2: Two-year estimated absolute risk reduction for vertebral and non-vertebral fracture.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Author</th>
<th>2-year * vertebral fracture risk in the placebo group (%)</th>
<th>2-year * ARR (%)</th>
<th>2-year non-vertebral fracture risk in the placebo group (%)</th>
<th>2 year * ARR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>Liberman 1995 [35]</td>
<td>4.1</td>
<td>2.0</td>
<td>6.4</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>Black 1996 [36]</td>
<td>10</td>
<td>4.7</td>
<td>9.8</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Cummings 1998 [37]</td>
<td>1.9</td>
<td>0.8</td>
<td>6.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Harris 1999 [38]</td>
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<td>3.4</td>
<td>5.6</td>
<td>2.1</td>
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<td></td>
<td>Register 2000 [39]</td>
<td>19.3</td>
<td>7.2</td>
<td>10.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Chesnut 2004 [40]</td>
<td>6.4</td>
<td>3.3</td>
<td>5.5</td>
<td>-0.6</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>Black 2007 [41]</td>
<td>7.7</td>
<td>5.5</td>
<td>7.1</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Lyles 2007 [42]</td>
<td>2.5</td>
<td>1.4</td>
<td>7.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Cummings 2009 [43]</td>
<td>4.8</td>
<td>3.3</td>
<td>5.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Ettinger 1999 [44]</td>
<td>6.7*</td>
<td>2.3</td>
<td>6.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Bazedoxifene</td>
<td>Silversmann 2008 [45]</td>
<td>2.8</td>
<td>1.2</td>
<td>4.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Neer 2001 [17]</td>
<td>14.3</td>
<td>9.3</td>
<td>5.5</td>
<td>2.9</td>
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</tbody>
</table>

* 2-year cumulative fracture risk were derived from the 3-year data assuming a linear relationship with time, except for the value with *, for which results are available in the publication. ARR = Absolute fracture Risk Reduction.

In conclusion, the bone anabolic effect of teriparatide is as-

Regarding the option of combined or sequential therapy with antiresorbers and bone anabolics, no trial exists with fracture as primary end point, and we are thus referring to surrogate parameters such as BMD and/or bone turnover markers.

Investigating the combined use of alendronate and teriparatide in men with osteoporosis, Finkelstein et al. found that alendronate started 6 months before introducing PTH blunted the ability of the latter to increase bone mineral density at the lumbar spine and the femoral neck in men with osteoporosis [24]. In 2010, they showed that the same could be observed in osteoporotic women [25]. In another trial, the effect of teriparatide on BMD following the use of raloxifene or alendronate was tested [28]. Teriparatide treatment stimulated bone turnover in patients pretreated with raloxifene or alendronate. However, prior treatment with alendronate retarded increases in BMD, whereas raloxifene allowed for the expected teriparatide-induced BMD increases comparable with those previously reported in treatment-naive patients. On the other hand, investigations on the effect of prior antiresorptive therapy on the BMD response to teriparatide showed that teriparatide treatment for 24 months was associated with a significant increase in spine BMD in patients with and without previous antiresorptive use [29]. In these trials, prior antiresorptive treatment modestly blunted the BMD response to teriparatide, especially during the first 6 months. At 12 months, the BMD of all groups had reached about the same level. For hip BMD, there was a tendency to lose some BMD in the first year of treatment, independently of prior antiresorptive therapy [30]. After this period, the effect of teriparatide on BMD was the same with our without previous antiresorptive use.

In contrast, Cosman et al. showed that the concomitant administration of intravenous zoledronic acid (5 mg) and daily subcutaneous teriparatide (20 µg) did not blunt the effect of the latter on spine BMD but resulted in a significantly greater increment in total hip BMD than teriparatide alone [26]. It should be noted that both therapies were ini-
tiated concomitantly. The combination of teriparatide and raloxifene increased bone formation to a similar degree as teriparatide alone [27]. However, the increase in bone resorption was significantly less and total hip BMD significantly increased for combination therapy compared with teriparatide alone.

The use of alendronate after parathyroid hormone (rhPTH 1-84) was investigated by Black et al. [31]. They found that after one year of parathyroid hormone, gains in BMD seemed to be maintained or increased with alendronate. But the gains were lost if parathyroid hormone was not followed by an antiresorptive agent.

Altogether, it appears that the response to teriparatide is impaired if the bone anabolic agent is introduced in patients treated with a bisphosphonate for several months. Thus, in regard to sequential therapy, pre-treatment with a bisphosphonate results in some delay of BMD response to teriparatide, followed by a catch-up. The combination of teriparatide with SERM’s or hormone replacement therapy appears to not impair the response to the parathyroid hormone. Finally, treatment with an antiresorptive drug after cessation of treatment with parathyroid hormone further improves BMD and could represent a suitable option.

In conclusion, the administration of teriparatide to patients on bisphosphonates appeared to be associated with a slightly blunted or retarded BMD response.

Conclusions

Based on the literature summarised above, the expert panel reached the consensus that the current limitation for prescription of teriparatide should be adapted, to allow the patients to benefit from the advantages of PTH given as a first line therapy in specifically selected patients characterised by a very high risk of fracture, thus deserving the deposition of new bone of optimal quality instead of the maintenance of bone mass it is achieved with antiresorptive drugs.

The following adaptations for postmenopausal women, for men and for patients with idiopathic or glucocorticoid-induced osteoporosis are recommended.

**Postmenopausal women:** Teriparatide should be indicated and prescribed as first-line treatment for postmenopausal women with two or more evident (Genant grade 2 or 3) vertebral fractures and a T-score ≤ -2.5 SD as well as in postmenopausal women with one evident (Genant grade 2 or 3) vertebral fracture and a T-score ≤ -3.5 SD.

**Men:** Teriparatide should be indicated and reimbursed as first-line treatment in men with two or more evident (Genant grade 2 or 3) vertebral fractures and a T-score ≤ -2.5 SD as well as in men with one evident (Genant grade 2 or 3) vertebral fracture and a T-score ≤ -3.5 SD.

**GIOP:** Teriparatide should be indicated and reimbursed as first-line treatment in patients with Glucocorticoid-induced osteoporosis with one evident (Genant grade 2 or 3) vertebral fracture or a T-score ≤ -2.5 SD.

This adaptation will help to select the most severely affected cases of osteoporosis for first line treatment with teriparatide. Therefore, it is unlikely that the rate of prescriptions will rise markedly.

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References


Figures (large format)

**Figure 1 A**

**Lumbar Spine**

(LS Mean % Change)

<table>
<thead>
<tr>
<th>Months</th>
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<th>6</th>
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<th>18</th>
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<td>184</td>
<td>173</td>
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<td>148</td>
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<tr>
<td>TPTD (n)</td>
<td>198</td>
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<td>178</td>
<td>170</td>
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<td>136</td>
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**Figure 1 B**

**Total Hip**

(LS Mean % Change)

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<tr>
<td>TPTD (n)</td>
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<td>156</td>
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**Figure 1 C**

**Femoral Neck**

(LS Mean % Change)

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<td>167</td>
<td>156</td>
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<td>120</td>
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</table>
Figure 1

Effects of Teriparatide or alendronate on BMD (A) or bone turnover markers (B) in patients with GIOP. The figures are from Saag et al. [23] with the permission of the publisher.