*Abaloparatide-SC paper v6.0*

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**The effect of abaloparatide-SC on fracture risk is independent of baseline FRAX fracture probability: a post hoc analysis of the ACTIVE study.**

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**Abstract**

Daily subcutaneous (SC) injections of the investigational drug abaloparatide-SC (80mcg) for 18 months significantly decrease the risk of vertebral and non-vertebral fracture compared with placebo in postmenopausal women. We examined the efficacy of abaloparatide-SC as a function of baseline fracture risk, assessed using the FRAX tool.

Baseline clinical risk factors (age, BMI, prior fracture, glucocorticoid use, rheumatoid arthritis, and smoking) were entered into country-specific FRAX models to calculate the 10-year probability of major osteoporotic fractures, with or without femoral neck BMD. The interaction between probability of a major osteoporotic fracture and treatment efficacy was examined by a Poisson regression.

821 women randomized to placebo and 824 women to abaloparatide-SC, mean age 69 years in both groups, were followed for up to 2 years. At baseline, the 10-year probability of major osteoporotic fractures (with BMD) ranged from 2.3-57.5% (mean 13.2%). Treatment with abaloparatide-SC was associated with a 69% (95%CI: 38, 85%) decrease in major osteoporotic fracture (MOF) and a 43% (95%CI: 9, 64%) decrease in any clinical fracture compared to placebo. For all outcomes, hazard ratios tended to decrease (i.e., greater efficacy) with increasing fracture probability. Whereas the interaction approached significance for the outcome of any fracture (p=0.11), there was no statistically significant interaction for any of the fracture outcomes. Similar results were noted when FRAX probability was computed without BMD.

Efficacy of abaloparatide-SC to decrease the risk of major osteoporotic fracture or any clinical fracture in postmenopausal women with low BMD and/or prior fracture appears independent of baseline fracture probability.

Introduction

Abaloparatide-SC is a 34 amino acid peptide with 71% homology with PTHrP(1-34) and 41% homology to PTH(1-34) that has been developed for subcutaneous delivery in the treatment of osteoporosis in postmenopasual women ([1](#_ENREF_1),[2](#_ENREF_2)). In a phase III, randomised placebo-controlled trial, Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE), in ambulatory postmenopausal female patients with osteoporosis, both abaloparatide-SC and teriparatide significantly decreased new vertebral fractures by 86% and 80%, respectively, whilst the relative risk reduction in nonvertebral fractures reached significance only for abaloparatide (43% vs. 28% for teriparatide) ([3](#_ENREF_3)). These effect sizes represent the average treatment effect and the question often arises if the effect is greater in sub-groups of patients with certain risk criteria. Sub-group analyses, especially those undertaken post hoc, decrease the study power while increasing the risk of type 1 errors([4](#_ENREF_4)). The use of analyses that examine for interactions using a continuous risk variable, such as baseline fracture probability, can reduce the impact of categorical sub-group analyses.

FRAX (http://www.shef.ac.uk/FRAX), the computer-based tool for assessment of fracture probability in men and women, was primarily developed to identify patients for treatment. However, several recent analyses have explored the interaction of treatment efficacy with pre-treatment fracture probabilities as assessed by FRAX ([5-8](#_ENREF_5)). For example, in post hoc analyses greater efficacy of treatment with increasing baseline FRAX fracture probability has been reported for clodronate ([8](#_ENREF_8)), whereas no interaction has been observed with raloxifene and strontium ranelate ([5](#_ENREF_5),[6](#_ENREF_6)). More relevant, perhaps, are two recent studies of teriparatide that also showed similar efficacy of teriparatide across the range of baseline fracture probabilities whether the drug was administered daily or weekly ([9](#_ENREF_9),[10](#_ENREF_10)). The aims of the present analysis were two-fold: to characterise the baseline fracture risk of those entering the ACTIVE study and, to determine whether the efficacy of abaloparatide-SC was independent of baseline fracture probability.

Methods

In the ACTIVE study, the effect of treatment (abaloparatide-SC 80mcg daily) on vertebral fracture incidence was compared to double-blind placebo or open-label treatment with subcutaneoaus teriparatide 20mcg daily([3](#_ENREF_3)). The study subjects comprised women age 50–85 years with a diagnosis of osteoporosis (BMD T-score ≤-2.5 and >-5.0 at the lumbar spine or femoral neck by DXA) and radiological evidence of two or more mild, or one or more moderate, vertebral fractures, or a history of low trauma forearm, humerus, sacral, pelvic, hip, femoral or tibial fracture within the past 5 years; women with more than four mild or moderate vertebral fractures or any severe vertebral fracture were excluded. Women over 65 years of age who met the fracture criteria but had a BMD T-score ≤-2.0 and >-5.0 were allowed to enroll. Women over 65 years of age who did not meet the fracture criteria but had a T-score ≤-3.0 and >-5.0 were also recruited.

All relevant individual-level data were provided by Radius Health, Inc. to the authors for this independent analysis. Data were provided on 1645 women aged 49-86 years who received abaloparatide-SC or placebo, with information on the clinical risk factors used in FRAX available in all, except for a parental history of hip fracture. Bone mineral density of the femoral neck at baseline was also available in 1642 patients. Data on fracture outcomes (patients with incident fractures) and treatment allocation were also transferred.

FRAX Assessment

Ten-year fracture probability was assessed with the FRAX® tool (version 3.9) in all patients blinded to any outcome variable. Both major osteoporotic fracture probability and hip fracture probability were chosen as risk variables. The estimate of probability can be used with clinical risk factors alone, or with femoral neck BMD and both outputs were calculated. The clinical risk factors included:

*A prior fragility fracture* – this variable was a composite of prior nonvertebral fracture (excluding skull, feet and hands) and a semi-quantitative radiographic assessment of vertebral fractures at baseline (T4-L4). Previous analyses of phase 3 studies have shown that grade 1 vertebral fractures ([11](#_ENREF_11)) are of no or limited prognostic value for nonvertebral fractures ([12](#_ENREF_12)) . A similar analysis undertaken in the ACTIVE confirmed this (Appendix); grade 1 fractures were therefore excluded in the base case analysis but were included in subsequent sensitivity analyses.

*Parental history of hip fracture* – this variable was not captured at entry to the study and was simulated based on examining the conditional probability of the association of a risk factor with age, BMI, and the dichotomous FRAX variables by logistic regression ([13](#_ENREF_13)). The associations were taken from the relationship between all clinical risk factors including BMI and femoral neck BMD in the cohorts with relevant information used to develop the FRAX model ([14](#_ENREF_14)). Baseline probabilities assuming a total absence of parental history of hip fracture (variable set to no for all participants) were used in the base case, but simulated values were included in sensitivity analyses.

*Current tobacco smoker* –a positive answer to a question enquiring about smoking of cigarettes or tobacco in the last 5 years was accepted as representing current smoker, as included in FRAX.

*Ever long-term use of oral glucocorticoids* – this was set to no for all participants as the use of oral glucocorticoids within the previous 12 months was an exclusion criterion for the study.

*Rheumatoid arthritis* – this was captured as a distinct variable based on the medical history.

*Secondary osteoporosis* - The presence of a cause of secondary osteoporosis was based on the medical history dataset and adjudicated by a study safety group. Causes of secondary osteoporosis included type 1 diabetes mellitus (n=1), malnutrition (n=1), liver disorders (n=29) and premature menopause (n=83). It should be noted that the secondary osteoporosis variable does not contribute to fracture probability when BMD is included in the calculation of FRAX. While increasing evidence suggests type 2 diabetes is a fracture risk factor, it is not yet a formal secondary cause within FRAX and its inclusion would not have allowed an equitable comparison of baseline probabilities with other studies in the literature. A total of 181 women were recorded to have type 2 diabetes with comparable numbers (88 and 93) in the placebo and abaloparatide-SC groups respectively.

*Daily alcohol consumption of 3 or more units*– a positive response (“Yes”) was assumed if a patient had answered the question “Amount of alcoholic drinks per week?” with 21 or more units; all other values were set to "No".

*Femoral neck BMD* - BMD values were supplied as absolute BMD values from the scanner together with the manufacturer. For BMD measured with Lunar Prodigy, the BMD was converted to Hologic values to remove the systematic differences between machine manufacturers ([15](#_ENREF_15)). A T-score was calculated using the NHANES reference values for young Caucasian women ([16](#_ENREF_16)) as used in FRAX ([14](#_ENREF_14)). For 3 patients with missing BMD tests, probabilities were only calculated without the inclusion of BMD and were excluded from analyses where FRAX was computed with BMD.

Country specificity - In addition to the dependence on clinical risk factors, fracture probability varies markedly in different regions of the world ([17](#_ENREF_17)) so that the FRAX models are calibrated to those countries where the epidemiology of fracture and death is known. FRAX models were available for all countries recruiting patients in the ACTIVE study. These included Argentina, Brazil, Czech Republic, Denmark, Estonia, Hong Kong, Lithuania, Poland, Romania and the US (ethnic specific models were available and used for the US).

Fracture outcomes - Depending on the skeletal site involved, incident fractures (regardless of the level of trauma) were variously categorized as any fracture (n=111), any osteoporotic fracture (excluding ankles, hands, feet, skull and face, n=82), major osteoporotic fractures (n=67), clinical vertebral fractures (n=13) and vertebral fractures assessed by morphometry (n=40). For the latter, it was assumed that the morphometric fractures had occurred half-way between the date of the x-ray finding and the prior x-ray.

Analytic approach

The effect of treatment was examined in an ITT analysis. For these analyses, the base case excluded the family history simulations and also excluded grade 1 baseline vertebral fractures, thus representing a more conservative approach. A Poisson model was used to study the relationship between age, the time since baseline, treatment, calculated 10-year probability on the one hand and on the other hand, the risk of fracture with only one fracture being counted per patient ([18](#_ENREF_18)). Here the person years were used (in contrast to a linear logistic model). The hazard function was assumed to be exp(β0 + β1 · current time from baseline + β2 · current age + β3 · 10-year probability + β4 · treatment + β5 · 10-year probability· treatment). The beta coefficientsreflect the importance of the variables as in a logistic model, and βx = 0 denotes that the corresponding variabledoes not contribute to fracture risk. The variable “10-year probability· treatment” tested for an interaction between efficacy and baseline 10-year probability, handled as a continuous variable, by determining if β5>0. Interactions other than 10-year probability· treatment, such as T-score · treatment, previous fracture · treatment, age · treatment were explored in sensitivity analyses.

Hazard ratios (HR) for treatment effect and 95% confidence intervals (95% CI) were computed as a continuous variable. For presentation, hazard ratios were shown at the 10th, 25th, 50th, 75th, and 90th percentile of fracture probability.

Results

Baseline characteristics and fracture probabilities

The baseline characteristics of the placebo and abaloparatide-SC groups at entry to the ACTIVE study are shown in Table 1. The mean probability of a major osteoporotic fracture, calculated with BMD, was 13.1% and 13.2% respectively in placebo and abaloparatide-SC arms. Just over half (55%) of the participants had a major osteoporotic fracture probability greater than 10%, while 15% were greater than 20%. The mean probability of a hip fracture was 4.7% and 4.9% respectively (Table 1). Fifty seven percent of the participants had a hip fracture probability greater than 3%, while approximately one third (34%) were greater than 5%. There were no significant differences among treatment arms concerning 10-year probability of hip or major osteoporotic fracture (p>0.20 for all comparisons).

Replication of efficacy analysis of abaloparatide

Compared to placebo, abaloparatide-SC decreased the risk of morphometric vertebral fractures by 86% - an effect that was statistically significant (Table 2). A similar reduction was observed on clinical vertebral fractures (88% reduction). Treatment was also associated with a significant 43% reduction in the risk of any clinical fracture, an effect that was enhanced when the analysis was confined to osteoporotic clinical fractures and major osteoporotic fractures (Table 2).

Interaction between treatment and FRAX fracture probability

In Table 3, the effects of abaloparatide-SC on the various categories of fracture outcomes according to the 10-year probability of a major osteoporotic fracture are shown where the baseline probability has been entered as a continuous variable in the model, which reduces the variance around the estimates. Note that clinical vertebral fractures are included in all the outcomes in Table 3 apart from the category of morphometric vertebral fractures. Confidence estimates for the hazard ratio crossed unity at all probabilities for clinical vertebral fractures. In contrast, the confidence estimates for the hazard ratio were at or well below unity across the range of probabilities for morphometric vertebral fractures. For all outcomes, hazard ratios tended to decrease (i.e., greater efficacy) with increasing fracture probability. Whereas the interaction approached significance for the outcome of any fracture (p=0.11), there was no statistically significant interaction for any of the fracture outcomes. The interaction between treatment effect and fracture probability for the outcome of major osteoporotic fracture is shown in Figure 1. Similar conclusions about interactions in the continuous models were derived when the simulated variables were included and/or when grade 1 vertebral fractures were included (data not shown). The interaction between treatment effect and fracture probability for the outcome of major osteoporotic fracture, based on tertile of baseline probability, is shown in Table 4. The sub-group analysis shows reductions in all tertiles but with wide confidence intervals and no significant interaction (p>0.30).

Suggested threshold fracture probabilities for inclusion into clinical trials by CHMP criteria are given as 15-20% for vertebral fracture, 5-7.5% for hip fracture and 10-15% for major non-vertebral fractures. In the case of hip fracture probability, more than one third of the women (34-37%, depending on whether probability calculated with BMD and/or simulated variables) recruited to the ACTIVE study exceeded the threshold risk of 5% with, as expected, a smaller proportion (18-21%) exceeding a threshold risk of 7.5%. For major osteoporotic fracture probability, 57% of the women lay over the threshold of 10% and 32% over the threshold of 15%. At a threshold of 10% and higher, there was a clear significant reduction in major osteoporotic fractures during abaloparatide-SC therapy (Figure 1).

Sensitivity analyses including other interactions (e.g. T-score · treatment, previous fracture · treatment, age · treatment) or the inclusion of the simulated history of parental fracture or grade 1 vertebral fractures had no significant impact on the results.

**Discussion**

It is an increasing trend, given the need for placebo-controlled registration studies, that the baseline fracture probabilities of recent studies are low when compared to earlier phase 3 studies in osteoporosis (Table 5). For example, at the 50th percentile of the distribution, the probability of a major osteoporotic fracture in the ACTIVE study was similar to that seen in the study of bazedoxifene ([7](#_ENREF_7)) but was somewhat lower than in studies of teriparatide ([9](#_ENREF_9),[10](#_ENREF_10)), clodronate ([8](#_ENREF_8)), strontium ([5](#_ENREF_5)) and raloxifene ([6](#_ENREF_6)). Notwithstanding, abaloparatide-SC therapy was associated with a significant reduction in fracture risk that was similar across a wide range of fracture probabilities; this implies that the intervention has efficacy in women at high risk, a requirement of the Committee for Medicinal Products for Human Use (CHMP) guidance ([19](#_ENREF_19)). The latter proposes thresholds of major osteoporotic fracture probability between 10-15% for clinical trial inclusion and it is clear from Figure 1 that abaloparatide is associated with significant fracture risk reduction in individuals with fracture risk at or above these values.

The findings from the present study can be placed within the context of retrospective assessments of other phase III studies. In a 3-year prospective, randomized, placebo-controlled trial of oral clodronate ([20](#_ENREF_20)), women aged 75 years or more living in the general community were given 800mg oral clodronate or matching placebo daily over three years. Greater clinical osteoporotic fracture reduction was seen at higher fracture probabilities, with or without the use of BMD, and efficacy was evident at fracture probabilities that exceeded 20% ([8](#_ENREF_8)). Similar findings of greater efficacy at higher probabilities, though without significant interactions, have been reported in analyses of the phase III studies of bazedoxifene ([21](#_ENREF_21)) and denosumab ([22](#_ENREF_22)). As in the case of clodronate, hazard ratios for the effect of bazedoxifene on all clinical fractures decreased with increasing fracture probability ([7](#_ENREF_7)), such that in patients with 10-year fracture probabilities at or above 16%, bazedoxifene was associated with a significant decrease in the risk of all clinical fractures ([7](#_ENREF_7)). In a pre-planned analysis of the FREEDOM trial, greater efficacy against fracture was shown in individuals at higher risk treated with denosumab ([22](#_ENREF_22)). In contrast, other studies have not shown this trend and, similar to abaloparatide-SC, have shown similar efficacy across a range of fracture probabilities (with greater absolute risk reductions in those at higher risk) ([5](#_ENREF_5),[6](#_ENREF_6),[9](#_ENREF_9),[10](#_ENREF_10)). For example, in a similar analysis of alendronate efficacy in the FIT trials, there was no evidence of an interaction between alendronate and baseline major osteoporotic fracture probability (with FN BMD) for the risk of non-vertebral fracture, clinical fractures, major osteoporotic fractures, and radiographic vertebral fractures([23](#_ENREF_23)). Nonetheless, the absolute benefit of alendronate was greatest among women with highest baseline fracture probability by FRAX.

This analysis has a number of strengths and limitations. The inclusion criteria for the study mean that it is difficult to generalize the observation of no apparent interaction to women with higher BMD or different fracture profiles. The fracture event rates are relatively low so that the power of the analysis to detect significant interactions is also reduced. For example, if a significant interaction for the outcome of any fracture existed between abaloparatide-SC efficacy and baseline fracture probability, then the observed p-value (p=0.11) suggests that we would need a 3.1 fold increase in the cohort size to show significance (p<0.05) at a power of 80% if everything (fracture rates, effect size and interaction etc) remained as reported in the current study. However, It is clear that our method of analysis, i.e. avoiding post hoc subgroup analysis by using a continuous variable such as FRAX probability, is a better approach than the use of categorical subgroups where the power to detect interaction is lower but paradoxically the chance of false positive results in sub-groups is higher ([24](#_ENREF_24)).

The lack of capture of information on a parental history of hip fracture meant that this variable had to be handled in a number of ways. Simulation was used to ensure that a potential history of parental hip fracture contributed to our estimate of the baseline risk profile of the study. Importantly, the use of the simulated population or the setting of parental history to “no” for all participants, did not impact on the conclusions drawn. This reflects the fact that the omission of parental history, or indeed the inclusion/exclusion of grade 1 vertebral fractures, is unlikely to bias any interactions between efficacy and fracture probability since the decision is likely to affect the placebo and treatment wings of the study equally.

In summary, despite a relatively low fracture incidence , the present analysis of the phase 3 ACTIVE study of abaloparatide-SC in postmenopausal women with low BMD and/or prior fracture shows efficacy of abaloparatide-SC for all fracture outcomes compared to placebo, with apparently similar efficacy across a wide range of baseline fracture risk.

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**Table 1** Baseline characteristics and ten-year probability (%) for hip fracture and a major osteoporotic fracture at entry to the ACTIVE study for the placebo and abaloparatide-SC groups, calculated with and without BMD. Values are means±SD, unless stated otherwise.

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **Placebo** | **Abaloparatide-SC** | **P-valuea** |
| Number | 821 | 824 |  |
| Age (y) | 68.7±6.5 | 68.9±6.5 | NS |
| BMI (kg/m2) | 25.1±3.6 | 25.0±3.5 | NS |
| Prior fracture (%) | 57 | 58 | NS**a** |
| Parental hip fracture (%)b | 6 | 6 | NS**a** |
| Glucocorticoid use (%)c | 0 | 0 | - |
| Rheumatoid arthritis (%)c | 0 | 0 | NS**a** |
| Smoking (%) | 11 | 13 | NS**a** |
| Alcohol (%) | 0 | 0 | NS**a** |
| Secondary osteoporosis (%) | 4 | 5 | NS**a** |
| Femoral neck BMD T-score | -2.15±0.68 | -2.16±0.63 | NS |
| FRAX MOF probability (no BMD) (%) | 13.1 ± 7.7 | 13.4 ± 8.5 | NS |
| FRAX Hip probability (no BMD) (%) | 5.0 ± 4.3 | 5.3 ± 5.3 | NS |
| FRAX MOF probability (+ BMD) (%) | 13.1 ± 7.7 | 13.2 ± 8.1 | NS |
| FRAX Hip probability (+ BMD) (%) | 4.7 ± 4.4 | 4.9 ± 5.0 | NS |

a Fishers permutation test; b Simulated for estimation of baseline probabilities only;

c Presence excluded patients from the trial; NS Not statistically significant

**Table 2.** Overall effects of abaloparatide-SC compared to placebo according to the fracture outcome selected. As described in the analytical approach, the analysis used a Poisson model.

|  |  |  |
| --- | --- | --- |
| **Fracture outcome** | **Overall treatment effect (HR, 95%CI)** | **Two-sided**  **p-values** |
| Any clinical fracture | 0.57, 0.36-0.91 | 0.019 |
| Osteoporotic fracture | 0.39, 0.21-0.70 | 0.0018 |
| Major osteoporotic fracture | 0.31, 0.15-0.62 | 0.001 |
| Clinical vertebral fracture | 0.12, 0.01-0.92 | 0.041 |
| Morphometric vertebral fracture | 0.14, 0.05-0.39 | <0.001 |

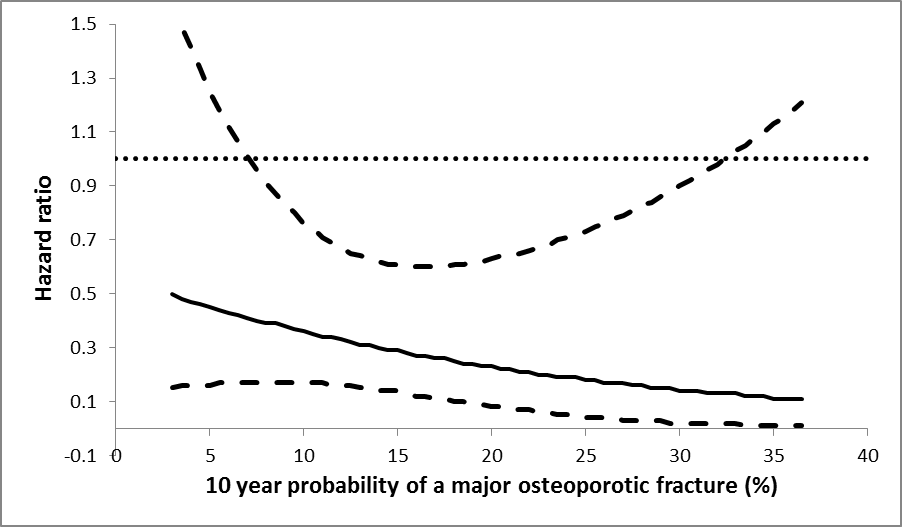
**Table 3.** Hazard ratio between treatments (abaloparatide-SC versus placebo) for all clinical, osteoporotic, major osteoporotic fractures, clinical and morphometric vertebral fractures at different values of 10-year probability (%) of a major osteoporotic fracture calculated with BMD.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Percentile | 10-year probability (%) | Any clinical fracture | Osteoporotic fracture | Major osteoporotic fracture | Clinical vertebral fracture | Morphometric vertebral fracture |
| 10th | 4.70 | 0.89 (0.45, 1.79) | 0.49 (0.20, 1.19) | 0.46 (0.16, 1.30) | 0.21 (0.01, 5.13) | 0.22 (0.05, 1.02) |
| 25th | 6.87 | 0.80 (0.44, 1.45) | 0.46 (0.21, 1.01) | 0.42 (0.17, 1.02) | 0.19 (0.01, 3.18) | 0.20 (0.05, 0.75) |
| 50th | 10.53 | 0.65 (0.40, 1.07) | 0.42 (0.22, 0.80) | 0.35 (0.17, 0.74) | 0.16 (0.02, 1.62) | 0.16 (0.05, 0.49) |
| 75th | 15.51 | 0.50 (0.30, 0.84) | 0.38 (0.20, 0.70) | 0.28 (0.13, 0.60) | 0.12 (0.02, 1.00) | 0.13 (0.04, 0.39) |
| 90th | 22.36 | 0.34 (0.15, 0.78) | 0.32 (0.13, 0.79) | 0.20 (0.06, 0.67) | 0.09 (0.01, 1.37) | 0.09 (0.02, 0.49) |
| p-value for interaction\* |  | 0.11 | >0.30 | >0.30 | >0.30 | >0.30 |

\*Two-sided p-value for interaction between treatment and FRAX

**Table 4.** Number of incident major osteoporotic fractures and hazard ratios between treatments (abaloparatide-SC versus placebo), classified by tertiles of baseline major osteoporotic fracture probability (MOF), calculated with BMD.

|  |  |  |  |
| --- | --- | --- | --- |
| **Tertiles of MOF probability** | **N** | **N with incident fractures** | **HR (95% CI)** |
| <8.47 | 547 | 10 | 0.27 (0.06-1.28) |
| 8.47-14.26 | 548 | 12 | 0.44 (0.13-1.46) |
| >14.26 | 547 | 22 | 0.27 (0.09-0.79) |

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**Figure 1**  Impact of abaloparatide-SC on major osteoporotic fracture compared to placebo, expressed as hazard ratio, across the range of major osteoporotic fracture probabilities at baseline. The interaction of efficacy with baseline probability was not significant (p>0.30).

**Table 5.** Summary of intervention studies that have examined the distribution of FRAX probabilities of a major fracture calculated with BMD (studies ranked by median probability)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Intervention | Percentile | | | | | Reference |
|  | 10 | 25 | 50 | 75 | 90 |  |
| Bazedoxifene | 2.8 | 4.5 | 8.2 | 14.5 | 21.7 | ([7](#_ENREF_7)) |
| Abaloparatide-SC | 4.7 | 6.9 | 10.5 | 15.5 | 22.4 | ACTIVE study |
| Clodronate | 10 | 12 | 16 | 22 | 30 | ([8](#_ENREF_8)) |
| Denosumab | 7.9 | 11.0 | 16.2 | 23.2 | 32.3 | Johansson\*\* |
| Teriparatide | 8.5 | 12.2 | 17.6 | 24.4 | 32.6 | ([9](#_ENREF_9)) |
| Raloxifene | 8.4 | 13.3 | 21.1 | 30.3 | 40.1 | ([6](#_ENREF_6)) |
| Strontium | 11.5 | 16.0 | 22.2 | 30.2 | 39.8 | ([5](#_ENREF_5)) |
| Teriparatide\* | 13.7 | 18.8 | 25.4 | 31.8 | 39.0 | ([10](#_ENREF_10)) |
| Alendronate | 14.2 | - | 27.7 | - | 49.1 | ([23](#_ENREF_23)) |

\*Weekly administration, \*\*Personal communication