Research Article

Prevention of aromatase inhibitor-induced bone loss with alendronate in postmenopausal women: The BATMAN Trial

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Abstract

Postmenopausal women on aromatase inhibitors (AI) are at risk of aromatase inhibitor-associated bone loss (AIBL) and fractures.

In 2005 Osteoporosis Australia proposed an algorithm for bisphosphonate intervention. Three hundred and three postmenopausal women with early breast cancer (EBC) were enrolled (osteoporotic, \( n = 25 \); osteopaenic, \( n = 146 \); normal bone mineral density (BMD), \( n = 126 \)). Weekly alendronate (70 mg) treatment efficacy as triggered by the algorithm in preventing bone loss was evaluated. All patients received anastrozole (1 mg daily), calcium and vitamin D.

Results:

All osteoporotic patients received alendronate at baseline. Eleven out of the 146 (7.5%) osteopaenic patients commenced alendronate within 18 months of participation and eleven commenced after. One hundred and twenty four out of the 146 (84.9%) osteopaenic patients and all 126 with normal baseline BMD did not trigger the algorithm.

At three years, lumbar spine mean BMD increased (15.6%, \( p < 0.01 \)) in the osteoporotic group. BMD in the osteopaenic group with early intervention significantly increased at three years (6.3%, \( p = 0.02 \)). No significant change was seen in the late intervention group. No change was observed in those with osteopaenia without alendronate.

There was a significant drop in lumbar spine (−5.4%) and hip (−4.5%) mean BMD, in the normal BMD group, none of whom received alendronate. Fracture data will be presented.

Conclusion: In postmenopausal women with endocrine-responsive EBC, BMD improved over time when a bisphosphonate is administered with anastrozole in osteoporotic patients using an osteoporosis schedule. Subjects with normal baseline BMD experienced the greatest BMD loss, although none became osteoporotic.

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1. Introduction

The cancer survival rates in Australia from 1998 to 2004 indicates that the majority of women diagnosed with breast cancer will survive over the long term with 88.0% alive at five years and 79.4% at ten years [1]. Extended survival exposes the majority of patients to the late effects of breast cancer therapies. Osteoporosis and the increased risk of associated skeletal related events are recognised as undesirable outcomes of various adjuvant therapies for early breast cancer [2]. Surveillance strategies for breast cancer need to incorporate monitoring for recurrence of disease as well as strategies to prevent and manage the bone related complications of adjuvant therapies.

Aromatase inhibitors in early breast cancer have demonstrated greater efficacy compared to tamoxifen in postmenopausal women with improved disease free survival, time to recurrence and time
to distant recurrence [3]. The suppression of oestrogen levels with AIs results in accelerated bone mineral loss and increased fracture risk. AIBL almost doubles the rate of loss seen in healthy postmenopausal women [4]. Results from the ATAC sub-study demonstrated that progressive AIBL occurs throughout the duration of AI treatment. This is greater in the lumbar spine in the first two years of therapy commencement and the decline appears to be less marked in years two to five of treatment but does not slow down in the hip [5].

In 2005, Osteoporosis Australia proposed an algorithm [6] to manage AIBL (Fig. 1). The algorithm assesses changes in bone mineral density (BMD) and N-telopeptide (NTx, a bone resorption marker) to determine timing of bisphosphonate therapy commencement. The Bisphosphonate and Anastrozole Trial – Bone Maintenance Algorithm Assessment (BATMAN) was designed to test the utility of this algorithm in postmenopausal women with hormone-receptor positive early breast cancer receiving adjuvant anastrozole, and the efficacy of intervention with alendronate, given in an osteoporosis schedule. Most studies in this area have excluded patients with osteoporosis due to the concern of worsening BMD. This study specifically addresses the issues of women with osteopenia and osteoporosis in this setting.

2. Patients and method

Eligible participants were postmenopausal women with Stage I–IIa hormone receptor positive breast cancer assessed as suitable for treatment with an aromatase inhibitor, specifically anastrozole. Postmenopausal status was defined as age ≥ 55 years with cessation of menstruation; < 55 years of age and no menses for 12 months; > 50 but < 55 and amenorrhoic (spontaneous, hysterectomy) and with postmenopausal gonadotrophin or oestradiol levels (luteinising hormone > 14 IU/L, follicle stimulating hormone levels > 40 IU/L, oestradiol < 110 pmol/L or according to the reference range for the laboratory involved); or bilateral oophorectomy. Following the observation of resumption of menses and reversal of menopause in a number of patients all of whom were under 50 years of age, we amended the entry criterion to exclude women under 50 years. Hormone replacement therapy must have been discontinued at least 2 weeks prior to registration. Other eligibility requirements were WHO performance status ≤ 2, with adequate renal and liver function. Patients receiving prior treatments with bisphosphonates and continuous systemic corticosteroids within the past 12 months were excluded. Any prior use of parathyroid hormone (PTH) for more than 1 week; systemic sodium fluoride for > 3 months during the past 2 years; any drugs known to affect the skeleton (eg. calcitonin, mithramycin, or gallium nitrate) were not allowed prior to and during the study. Patients with history of diseases with influence on bone metabolism (e.g. Paget’s disease, Osteogenesis Imperfecta, and primary or secondary hyperthyroidism), lactose intolerance, delayed oesophageal emptying; previous or concomitant malignancy within the past 5 years, were also excluded. Patients with a fracture due to minimal trauma that was detected on baseline radiology were excluded from the study.

Written informed consent was obtained from each patient before inclusion. The study was approved by the Barwon Health Human Research Ethics Committee (HREC), Eastern Health HREC, St Vincent’s HREC, North Coast Area Health Service HREC, and Sydney South West Area Health Service HREC. Eight Australian oncology centres participated. These centres included Barwon Health, St John of God Healthcare Geelong, South West Healthcare (Warrnambool), Box Hill Hospital, Maroondah Hospital, St. Vincent’s Hospital Melbourne, Tweed Hospital and Royal Prince Alfred Hospital.

The study was conducted in accordance with the National Health and Medical Research Council’s National Statement on Ethical Conduct in Research Involving Humans (June 1999) and the CPMP/ICH Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

Osteoporosis was defined as BMD 2.5 standard deviations or more below the reference range mean for young adults. Osteopenia being those with a BMD between 1 and 2.5 standard deviations below the young adult mean [7]. Lumbar spine (L2-L4) and femoral neck BMD was quantified with Lunar DPX-L (Lunar, Madison, WI, USA), GE-Lunar Prodigy (Prodigy; GE Lunar, Madison, WI, USA) or Norland Excell™ machines. Dual-energy X-ray absorptiometry (DXA) at baseline, 1, 2 and 3 years assessed using Norland machines were converted to Lunar equivalents using the Genant conversion equations [8]. N-telopeptide (NTx) is a marker of bone resorption. Urine samples for urinary N-telopeptide (uNTx) were collected at baseline, and at 6 months before inclusion. The study was approved by the Barwon Health Human Research Ethics Committee (HREC), Eastern Health HREC, St Vincent’s HREC, North Coast Area Health Service HREC, and Sydney South West Area Health Service HREC. Eight Australian oncology centres participated. These centres included Barwon Health, St John of God Healthcare Geelong, South West Healthcare (Warrnambool), Box Hill Hospital, Maroondah Hospital, St. Vincent’s Hospital Melbourne, Tweed Hospital and Royal Prince Alfred Hospital.

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All patients were commenced on oral anastrozole 1 mg daily, calcium (≥ 500 mg per day) and Vitamin D (≥ 400 IU daily) supplements. No dose modifications were permitted for the duration of the study for those receiving either anastrozole or alendronate.

In accordance with the OAA, patients with a BMD T-Score below -2.5 S.D. at either the lumbar vertebra or femoral neck at
any time-point, were commenced on alendronate 70 mg oral weekly. Patients with a T-score between −2.0 S.D. and −2.5 S.D. commenced alendronate if the index of bone mineral turnover was elevated >20% at the 6-month time-point. If the BMD T-Score fell below −2.0 S.D. at either the lumbar vertebra or femoral neck at any time during the five-year treatment period, bone mineral turnover studies were instituted. If the bone mineral turnover studies indicated that the biochemical marker (uNTx) was elevated more than 20% over baseline, then bisphosphonate therapy was instituted.

Patients were reviewed at 3 monthly intervals in years one and two, and 6 monthly until year 5 with clinical examination and a yearly mammogram. In this 3-year analysis, we assessed the change in both lumbar vertebra (L2 to L4) and femoral neck BMD at 12 monthly intervals. We also assessed the benefit of alendronate with respect to uNTx and BMD in protecting bone health. The clinical fracture incidence cumulative over 3 years was evaluated.

Different influences on lipid profiles have been observed in trials comparing aromatase inhibitors to tamoxifen [9]. For safety reasons, a fasting lipid assessment (LDL, HDL, total cholesterol and triglycerides) was measured at baseline and repeated at the 6-month trial visit for all participants. Vitamin D level was measured at baseline.

3. Statistical analysis

BMD was analysed using a repeated measures model that implicitly allowed for missing data and assessed dependent samples over time with the multiple comparison Tukeys test applied. The level of significance was set at $p = 0.05$.

4. Results

4.1. Study population

Between September 2005 and June 2010, 303 patients from 8 Australian centres were enrolled, 297 were eligible for the study (Fig. 2). At baseline, 25 (8.4%) were classified as having osteoporosis, 146 (49.2%) were osteopaenic and 126 (42.1%) patients had normal BMD. All of the 25 osteoporotic patients commenced alendronate at baseline. Twenty-two osteopaenic patients were determined by the algorithm to be eligible for alendronate during the trial period but 1 patient refused. One osteopaenic patient received alendronate off trial after a non-traumatic fracture. One hundred and twenty four osteopaenic patients did not require alendronate. Only 2 of the patients with normal BMD were treated with alendronate, after a clinical fracture event, without triggering the algorithm and were excluded from this time point.

Table 1 shows the baseline characteristics of the study population. Patients in the normal baseline BMD subgroup tended to be younger. The mean age was higher for the patients in the early intervention (≤18 months from commencing alendronate) osteopaenic group in comparison to the late intervention (≥18 months) group. BMD was higher in the osteopaenic group that received late and no intervention. In the osteopaenic subgroup, there were 2 patients that had previous axillary clearance for a prior breast cancer and hence lymph node stage was not determined for the current breast cancer. All patients’ tumours were oestrogen receptor (ER) and/or progesterone receptor (PR) positive.

4.1.1. BMD results

4.1.1.1. Osteoporotic patients. BMD of the spine at baseline was $0.914 \pm 0.028$ g/cm$^2$ (mean ± SE) and significantly increased to
4.1.1.3. Osteopaenic patients with alendronate (early intervention).

BMD of the hip was 0.847 ± 0.014 g/cm² at 1 year, 0.888 ± 0.015 g/cm² at 2 years and 1.000 ± 0.021 g/cm² at 3 years. Similarly, BMD of the hip was 0.956 ± 0.011 g/cm² (2 years) and 0.956 ± 0.013 g/cm² (3 years) with a decrease of 2.5% (p < 0.01), 4.6% (p < 0.01) and 4.5% (p < 0.01), respectively, (Fig. 4e). No patients in this subgroup became osteoporotic.

4.1.1.4. Osteopaenic patients without alendronate.

BMD of the spine at baseline was 1.112 ± 0.012 g/cm² (mean ± S.E) at baseline, 1.097 ± 0.014 g/cm² at 1 year, 1.088 ± 0.015 g/cm² at 2 years and 1.100 ± 0.021 g/cm² at 3 years, (Fig. 3d). This equates to a non-significant decrease of 1.3%, 2.2% and 1.0% respectively, from baseline. Similarly, BMD of the hip was 0.847 ± 0.006 g/cm² (baseline), 0.834 ± 0.008 g/cm² (1 year), 0.830 ± 0.009 g/cm² (2 years) and 0.830 ± 0.008 g/cm² (3 years) with a decrease of 1.5% (p = 0.18), 2.0% (p = 0.04) and 1.7% (p = 0.25), respectively, (Fig. 4d).

4.1.1.5. Patients with normal BMD. BMD of the spine at baseline was 1.263 ± 0.011 g/cm² (mean ± SE) and significantly decreased to 1.219 ± 0.013 g/cm² at 1 year (p = 0.03), 1.224 ± 0.017 g/cm² at 2 years (p = 0.07) and 1.195 ± 0.016 g/cm² at 3 years (p < 0.01), (Fig. 3e). This equates to a decrease of 3.5%, 3.1% and 5.4% respectively, from baseline. Similarly, BMD of the hip was 1.001 ± 0.008 g/cm² (baseline), 0.972 ± 0.009 g/cm² (1 year), 0.956 ± 0.011 g/cm² (2 years) and 0.956 ± 0.013 g/cm² (3 years) with a decrease of 2.5% (p < 0.01), 4.6% (p < 0.01) and 4.5% (p < 0.01), respectively, (Fig. 4e). No patients in this subgroup became osteoporotic.

4.1.1.6. Three year non traumatic fracture rates. There was 1 (3.85%) non-traumatic fracture in the osteoporotic subgroup over the 3 years period. There were no non-traumatic fractures in the osteopaenic subgroup that received alendronate. The osteopaenic subgroup that did not have alendronate had 10 (8.06%) non-traumatic fractures over 3 years. 2 (15.9%) non-traumatic fractures were documented in the normal BMD group.

4.1.1.7. Markers of bone turnover. The osteopaenic subgroup commencing alendronate at baseline demonstrated a drop in uNTx of 38% after 6 months of treatment. No patients in the osteopaenic and normal BMD subgroups received alendronate in the first 6 months. Their uNTx had increased by 24% and 51%, respectively.

4.1.1.8. Vitamin D levels. Vitamin D levels were checked at baseline in 291 of the 297 eligible patients. 34% (99/291) of patients had a baseline vitamin D level < 50 nmol/L consistent with vitamin D deficiency (Fig. 5). 3.4% (10/291) patients had moderate to severe vitamin D deficiency (< 25 nmol/L). The majority (75%) of patients were recruited from southern
Victoria with an approximate latitude of 38°S. The remaining 72/291 patients were from more northerly states with latitudes of 33.9°S (Sydney) and 28.2°S (Tweed Heads). The mean vitamin D levels were 62.13, 48.5 and 61.47 (nmol/L) respectively. Data was adjusted for age and the season during which the measurements were taken.

4.1.1.9. Lipid. There was no significant change in the lipid profile after 6 months of anastrozole.

4.1.1.10. Reason for discontinuation. 78 participants withdrew from the study by 36 months.

Most (39.7%) patients withdrew from the study due to anastrozole-related adverse events (AEs), which included myalgias, arthralgias, hot flushes, tenosynovitis and fractures (Table 2). Only 5 patients withdrew due to bisphosphonate-related AEs, which were largely due to gastrointestinal side effects. There were no cases of osteonecrosis of the jaw. Four patients had less than 12 months, and a further fifty between 12 and 24 months follow up. Nine (3%) patients experienced

Fig. 3. Mean change (g/cm²) in lumbar spine BMD in (a) osteoporotic subgroup (n=25), (b) osteopaenic subgroup with early alendronate, n=11, (c) osteopaenic group with late alendronate (n=11), (d) osteopaenic group without alendronate (n=124) and (e) normal BMD subgroup (n=126).
return of ovarian function while on anastrozole, necessitating discontinuation of their trial participation. They were all aged ≤ 50 years and most of these had experienced chemotherapy-induced menopause.

5. Discussion

Based on the results of this three-year analysis, alendronate effectively increases BMD in osteoporotic, postmenopausal women with early breast cancer who are receiving adjuvant therapy with anastrozole. This subgroup of women would have the greatest risk of bone loss and fracture. The benefit seen with bisphosphonate therapy was greater at the spine than at the hip but did significantly improve both spine and hip BMD (15.6%, p < 0.01 and 5.6%, p < 0.01 at 3 years respectively). Prior studies, such as Z-FAST [10], have mostly reported the impact of bisphosphonates on BMD in women with osteopenia. Our findings are consistent with the results from the ARIBON trial that included 13 osteoporotic women who received anastrozole and ibandronate contributing to an increased BMD of 3.52% and 2.49% for

![Fig. 4. Mean change (g/cm²) in hip BMD in (a) osteoporotic subgroup (n=25), (b) osteopaenic subgroup with early alendronate (n=11), (c) osteopaenic group with late alendronate (n=11), (d) osteopaenic group without alendronate (n=124) and (e) normal BMD subgroup (n=126).](image-url)
the lumbar spine and hip at 2 years [11]. Subsequent results of this study continue to show an increase in lumbar BMD (9.65%) and at the hip (2.72%) for the 9/13 patients in the osteoporotic group when assessed at their 5 year follow-up, demonstrating the ability to use AI therapy currently with a bisphosphonate in these women [12]. Our study also confirms the safety of commencing aromatase inhibitors in this frequently excluded sub-group.

BMD of the spine, but not at the hip, demonstrated a significant increase of 6.3%, \(p=0.02\) at 3 years in the osteopaenic group receiving early intervention with alendronate. However, we did not demonstrate an improvement in BMD for the osteopaenic group receiving late intervention with alendronate. Patient numbers were small and larger benefit might be expected with longer follow-up of these patients. These late intervention patients triggered the algorithm and started on alendronate at different time points (<18 months; 18–24 months; 24–36 months; >36 months). This results in a confounding proportion of patients within this group with ongoing BMD loss prior to starting bisphosphonate therapy.

The mean time to the introduction of alendronate was 21.5 months in the osteopaenic group. With this delay in institution of alendronate there has been limited observation time post-intervention. An additional reason for the small or lack of demonstrable benefit from early and late alendronate in the osteopaenic group respectively, is our use of the baseline BMD as the comparator. This introduces a bias against the therapy BMD end point, as the BMD further reduced prior to the intervention. Perhaps with a longer follow-up period of 5 years this may allow better demonstration of the protective effect of bisphosphonate therapy.

In the normal BMD subgroup, there was progressive bone loss over 3 years at the spine and hip (5.4% and 4.5%, respectively). This finding is consistent with the ATAC data [5]. Two patients required alendronate triggered by clinical events but there were no algorithm triggered events. There were no non-traumatic fractures reported in the osteopaenic group receiving alendronate compared with 8% in the group without alendronate. The osteoporotic patients would be presumed to have a higher fracture rate than the osteopaenic group associated with lower baseline BMD. The non-traumatic fracture rate in the osteoporotic group receiving alendronate was lower in comparison to the osteopaenic group without alendronate. Overall this suggests a protective effect of alendronate. However, these results should be interpreted with caution because the study was not adequately powered to detect a difference in fracture rates.

Eleven osteopaenic patients progressed to osteoporosis with \(T\) scores \(\leq -2.5\) but this was not observed for patients with a normal baseline BMD. The intervention rate, with the Osteoporosis Australia Algorithm, for introducing alendronate to the patients with osteopaenia (15.1%) was lower than we had expected. Given that 27% of Australian women aged 60 and over are considered osteoporotic and 51% [7] are osteopaenic, it was expected that approximately 75% of women accrued would require bisphosphonate therapy. The high rate, 8%, of low trauma fractures we observed in osteopaenic patients without alendronate suggests that the algorithm threshold may be set too high in this group. In the ATAC study, fracture rates were constant during the period of treatment [9]. More fractures were reported in the

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**Table 2**

| Reason for discontinuation          | Osteoporotic with alendronate \(n=25\) | Osteopaenic with alendronate \(n=22\) | Osteopaenic without alendronate \(n=124\) | Normal BMD \(n=126\) |
|------------------------------------|---------------------------------------|--------------------------------------|-------------------------------------------|---------------------|
| Number of discontinuations         | \(n=5\) (20%)                         | \(n=5\) (22.7%)                      | \(n=36\) (29%)                            | \(n=32\) (25.4%)    |
| AI related AE                      |                                       |                                      |                                           |                     |
| Bisphosphonate related AE          | 2                                     | 1                                    |                                           |                     |
| Relapse/recurrence                 | 1                                     | 2                                    |                                           |                     |
| PI decision                        | 1                                     | 2                                    |                                           |                     |
| Death                              |                                       |                                      |                                           |                     |
| Other                              | 2                                     | 1                                    | 8                                         | 12                  |

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**Fig. 5.** Baseline vitamin D level for the osteoporotic, osteopaenic and normal BMD subgroups.
anastrozole than tamoxifen group but then were similar after the completion of treatment. There was no protocol for bone health maintenance in this study and bisphosphonate use was low at 10% and 7% in these groups respectively [3].

Our patients in the osteopaenic group receiving early intervention had a mean BMD of 1.009 g/cm², equivalent to a T-score of –1.7. The ATAC sub-study found that 5 women with osteopoenia at baseline (4 in the anastrozole group and 1 receiving tamoxifen) developed osteoporosis. They evaluated the T-scores from baseline to 5 years with linear regression, and found that a T-score of –1.5 may define risk for the development of osteoporosis as no patients with a higher T-score dropped to –< 2.5 on treatment [5].

The UK expert group have suggested an alternative algorithm. In postmenopausal women with a T-score that falls below –2.0 or if the rate of bone loss is more than 4% per year with pre-existing osteopenia, a bisphosphonate is recommended [13]. This pragmatic recommendation avoids the need to measure uNTx which is expensive and unwieldy. A simplified algorithm, omitting uNTx but taking into account major risk factors for osteoporotic fracture may have more clinical utility.

Vitamin D deficiency is common in our community and contributes adversely to bone health, and to breast cancer outcomes. It is associated with reduced BMD and osteoporosis. Although most studies focused on the elderly population, appropriate vitamin D supplementation is an important modifiable risk factor for reducing falls and fractures [14]. All the participants in our trial received 400–500 IU of oral vitamin D daily regardless of their baseline vitamin D levels. One third of our patients had vitamin D deficiency. We did not see a gradient in mean vitamin D levels between patients from more northerly states and Southern Victoria. This high level of vitamin D deficiency in our patients is comparable to that found in our community regardless of season and latitude. The reported prevalence of vitamin D insufficiency (≤ 50 nmol/L) in women during winter/spring was 40.5%, and 37.4% in southeast Queensland (latitude 28.2°S), and Geelong (38°S) [15]. According to the Working Group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia, higher doses of vitamin D up to 3000–5000 IU daily for 6–12 weeks are required to replete body stores, followed by 1000 IU daily as maintenance [16]. Treatment of vitamin D deficiency was a decision of the investigator clinician.

Our analysis also showed that there were no meaningful lipid changes with anastrozole, as a surrogate for cardiovascular health. This is in keeping with the TEAM Japan [17], TEAM Greek [18] sub-studies and the SABRE trial [19], which showed that AIs have no detrimental effects on lipid parameters. This is reassuring when using AIs in women with favourable prognosis breast cancer.

Three percent of the participants reported return of ovarian function while receiving adjuvant anastrozole. This raises concern that these patients were exposed to a period of inadequate adjuvant therapy as the anticancer effects from AIs would be abrogated due to return of ovarian production of oestradiol. AI’s may in fact induce ovulation [20], Smith et al. suggested guidelines for patients with chemotherapy induced amenorrhoea recommending that women < 40 years old should not receive an AI alone as adjuvant treatment [21]. These guidelines were not published prior to the commencement of the trial. For women older than 40 years, it was suggested that serial monitoring of sexual hormone levels should be performed and requires a sensitive assay. We have observed reversal of chemotherapy-induced menopause in patients up to age 49 years. An alternative is to use tamoxifen alone, with the option of a later switch or an AI with concurrent ovarian function suppression. Women in this age group should be informed of the possibility of return of ovarian function and to report menstrual bleeding or the cessation of hot flushes to their treating oncologists [21]. The reversals of ovarian function were all in women under 50, and we amended the entry criterion to exclude this age group.

6. Conclusions

Aromatase inhibitor induced bone loss is less dramatic than expected, can be managed and does not contraindicate AI use. Osteoporosis dose intensity bisphosphonates are sufficient for these patients in regard to bone health [22]. The Osteoporosis Australia algorithm proved cumbersome involving expensive biochemical tests of bone turnover, and has a high threshold. A simpler algorithm with a T score threshold of –2.0 as stated in the UK recommendation may be clinically useful.

This study confirms that it is safe to prescribe anastrozole in osteoporotic post-menopausal women with early breast cancer, when used together with a bisphosphonate. No patient with normal baseline BMD became osteoporotic. A randomised controlled study would need to be performed to validate these results given some subgroups had small patient numbers.

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This research was conducted with support from the Investigator-Sponsored Study Program of Astra Zeneca. The authors were responsible for interpretation of the data and writing of the manuscript.

Conflict of interest statement

The authors declare that there are no conflicts of interest. Chooi Lee is an employee of Boehringer Ingelheim Ltd, UK. This study was supported by an untied grant from AstraZeneca.

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Professor Philip Sambrook passed away in 2012. He contributed to the concept, design and conduct of the BATMAN study.

Appendix A

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