Prevention of Anastrozole-Induced Bone Loss with Monthly Oral Ibandronate during Adjuvant Aromatase Inhibitor Therapy for Breast Cancer

James E. Lester,1 David Dodwell,3 Omprakash P. Purohit,1 Sandra A. Gutcher,1 Susan P. Ellis,1 Ruth Thorpe,3 Janet M. Horsman,1 Janet E. Brown,4 Rosemary A. Hannon,2 and Robert E. Coleman1

Abstract

Purpose: The aromatase inhibitor anastrozole is a highly effective well-tolerated treatment for postmenopausal endocrine-responsive breast cancer. However, its use is associated with accelerated bone loss and an increase in fracture risk. The ARIBON trial is a double-blind, randomized, placebo-controlled study designed to evaluate the impact of bisphosphonate treatment on bone mineral density (BMD) in women taking anastrozole.

Experimental Design: BMD was assessed in 131 postmenopausal, surgically treated women with early breast cancer at two U.K. centers. Of these, 50 patients had osteopenia (T score -1.0 to -2.5) at either the hip or lumbar spine. All patients were treated with anastrozole 1 mg once a day and calcium and vitamin D supplementation. In addition, osteopenic patients were randomized to receive either treatment with ibandronate 150 mg orally every month or placebo.

Results: After 2 years, osteopenic patients treated with ibandronate gained +2.98% (range -8.9, +19.9) and +0.60% (range -9.0, +6.9) at the lumbar spine and hip, respectively. Patients treated with placebo, however, lost -3.22% (range -16.0, +4.3) at the lumbar spine and -3.90% (range -12.3, +7.2) at the hip. The differences between the two treatment arms were statistically significant at both sites (P < 0.01). At 12 months, urinary n-telopeptide, serum c-telopeptide, and serum bone–specific alkaline phosphatase levels declined in patients receiving ibandronate (30.9%, 26.3%, and 22.8%, respectively) and increased in those taking placebo (40.3%, 34.9%, and 37.0%, respectively).

Conclusions: Monthly oral ibandronate improves bone density and normalizes bone turnover in patients treated with anastrozole.

In the last few years, aromatase inhibitors have emerged as an alternative to tamoxifen for the adjuvant treatment of estrogen receptor–positive early breast cancer in postmenopausal women. Several large randomized clinical trials (1–4) have shown that the use of an aromatase inhibitor for 5 years is superior to tamoxifen in terms of disease-free survival and time to recurrence. As a result, many centers would now consider an aromatase inhibitor as first-line treatment for postmenopausal patients. However, the long-term effects of profound estrogen suppression in patients, who may be cured from their cancer, is of concern.

Three third-generation aromatase inhibitors, anastrozole, letrozole, and exemestane, are currently available. Each of these agents is associated with declines in serum estrogen to almost unrecordable levels (5–7). Circulating estrogen levels have profound effects on bone physiology, and low residual postmenopausal estrogen levels have been shown in normal women to be associated with an increase in fracture risk (8).

Additionally, in the adjuvant setting, the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial has shown a significant advantage for anastrozole over tamoxifen (1). A recent update has shown not only an improvement in disease-free survival but also a reduction in distant metastases (1). Consequently, the American Society of Clinical Oncology has endorsed the use of anastrozole in the adjuvant treatment setting (9).

The ATAC trial also showed a favorable adverse event profile for anastrozole, compared with tamoxifen, with the exception of effects on the musculoskeletal system. In the anastrozole group, there were more musculoskeletal side effects and fractures, most frequently affecting the spine and sites other than the hip and wrist. The incidence of all fractures after 5 years’ treatment was 11% in the anastrozole group and 7.7% in the tamoxifen group (P < 0.0001; ref. 1).

In the ATAC trial, bone subprotocol patients treated with anastrozole lost 2.3%, 4.0%, and 6.1% bone mineral density (BMD) at the lumbar spine (LS) and 1.5%, 3.9%, and 7.2% at...
the hip (TH) after 1, 2, and 5 years, respectively ($P < 0.001$; ref. 10). Strategies are therefore urgently needed to determine how best to monitor and treat these patients, especially those with preexisting osteopenia or osteoporosis.

Bisphosphonates are the cornerstone of management in postmenopausal osteoporosis with randomized trial evidence of reductions in vertebral fractures for ibandronate (11) and both vertebral and nonvertebral fracture rates for alendronate (12), risedronate (13), and zoledronic acid (14). Ibandronate is a highly potent nitrogen-containing bisphosphonate that can be administered both i.v. and orally. Using the oral route of administration, a single dose every month in postmenopausal women with osteoporosis (PMO) led to similar changes in BMD and bone turnover markers as daily treatment (15). This simple treatment is potentially highly attractive for cancer patients and offers an alternative to i.v. treatment (16, 17) or weekly oral therapy.

In this randomized placebo controlled trial, we have evaluated the impact of oral ibandronate (Bondronat), using the usual PMO schedule of 150 mg once a month on BMD in women with osteopenia taking anastrozole. Additionally, we have assessed changes in levels of biochemical markers of bone metabolism and related short-term (3-month) marker changes with subsequent changes in BMD.

### Materials and Methods

The study included postmenopausal women with a histologically confirmed diagnosis of estrogen receptor–positive breast cancer. Patients were excluded if their menopause was induced by either prior chemotherapy or by drug therapy. Other exclusion criteria included concurrent administration of medication(s) with effects on bone such as bisphosphonates or hormone replacement therapy, abnormal renal function, disorders of bone metabolism, and previous bilateral hip fractures or bilateral hip prostheses that would have made BMD assessments impossible.

Consecutive eligible patients were approached and, following informed consent, underwent a baseline assessment of BMD at the LS and TH before both commencing anastrozole and study entry. All patients received anastrozole 1 mg once a day and calcium (500 mg) and vitamin D (400 IU) supplements daily.

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**Fig. 1.** Consort diagram showing the number of patients recruited and those included in the analysis.
Patients with normal BMD (T score > -1 at both the LS and TH) were allocated to an observation group with a follow-up BMD assessment at 2 y. Patients with osteoporosis (T score < -2.5 at either the LS or TH) received open-label ibandronate 150 mg every 28 d orally. Patients classified as osteopenic (T scores of > -2.5 and < -1.0 either at the LS and TH) were randomized to receive either ibandronate tablets 150 mg every 28 d orally or placebo tablets of identical appearance also every 28 d orally for 2 y. It is this randomized group that is the subject of this report. The CONSORT diagram in Fig. 1 shows the disposition of patients at baseline and their subsequent course on study.

Ibandronate/placebo capsules were taken in an upright position first thing in the morning on an empty stomach and washed down with 100 mL water to minimize the risk of esophageal irritation; no food or drink (other than water) was consumed for at least 30 min after taking the study medication.

Upon randomization, patients were stratified according to center, number of years since menopause (less than versus greater than 5 y), prior chemotherapy (yes versus no), and prior hormone replacement therapy (yes versus no). The primary end point was the change in BMD at the LS and TH at 1 and 2 y for the anastrozole plus ibandronate–treated patients compared with those receiving anastrozole plus placebo. Secondary end points included the changes in bone resorption and formation markers over time and adverse events, including any fracture with and without osteoporosis.

Follow-up LS and TH BMD scans were repeated after 1 y (12 ± 1 mo) and 2 y (24 ± 2 mo). Patients who developed osteoporosis while taking ibandronate/placebo medication were unblinded and offered open-label ibandronate treatment.

Throughout the study, the same densitometer was used at each of the two centers to optimize the measurements. A phantom spine was scanned on a minimum of 3 d/wk in each center to ensure precision over time. T score results were calculated using the Lunar (DPX Series Operator’s Manual 1998) manufacturer’s reference ranges for the lumbar spine (L2-L4) and the NHANES III reference range for the total hip region.

Serum and urine samples were collected at baseline and at 3, 6, and 12 mo for the estimation of bone alkaline phosphatase (sBALP) and type 1 collagen cross-links. For urinary n-telopeptide measurements (uNTX), the second voided urine of the day was collected and the concentration of uNTX was expressed as a ratio to urinary creatinine. For serum c-telopeptide (sCTX) and sBALP, a 10-mL fasting blood sample was taken at the same time of day for each visit and the time was recorded. Serum was stored at less than -70°C until analysis.

Urinary cross-linked NH2-terminal peptides of type I collagen (NTX) were measured by a chemiluminescent competitive assay on Vitro Eci autoanalyzer (Ortho-Clinical; CV 3.7%) and expressed as a ratio to urinary creatinine, which was measured by an automated dry slide method (Vitros 250, OrthoDiagnostics; CV 1.1%). The between-assay CV for NTX was 3.7% and the between-assay CV for the creatinine measurement was 1.1%.

Serum cross-linked C telopeptides of type I collagen (sCTX) were measured with the Crosslaps enzyme-linked immunosassay (Nordic Bioscience Diagnostics A/S). Samples were measured in duplicate and the within assay CV was 2.4% and the between-assay CV was 2.5%.

Serum BALP was measured by the Ostase assay, a paramagnetic chemiluminescent method on an Acess autoanalyzer (Beckman Coulter, Inc). The between-assay CV was 6.4%. All samples for the same individual were analyzed in the same analytical batch.

Full local ethics committee approval was successfully obtained in both centers recruiting patients for the study.

Compliance of study medication was discussed at each study visit and the number of missed doses was recorded. Bone marker measurements also provided an indirect assessment of compliance.

**Statistical power and analysis.** A total of 20 osteopenic patients per treatment arm were required to provide 90% power to detect a mean percentage difference in BMD between the two groups of 4%, a value that corresponds with the expected increase in BMD with oral

### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Osteopenic (n = 25)</th>
<th>Placebo (n = 25)</th>
<th>Normal (n = 68)</th>
<th>Osteoporotic (n = 13)</th>
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<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Median (IQR)</td>
<td>67.8 (58.9, 73.4)</td>
<td>67.5 (63.6, 71.0)</td>
<td>63.0 (58.8, 68.1)</td>
<td>68.2 (63.2, 75.9)</td>
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<td>Lumbar spine BMD</td>
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<td>Median T score (IQR)</td>
<td>-1.4 (-1.6, -1.2)</td>
<td>-1.2 (-1.7, -0.8)</td>
<td>+0.2 (-0.3, 1.2)</td>
<td>-2.6 (-3.4, -2.5)</td>
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<td>Total Hip BMD</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Median T score (IQR)</td>
<td>-1.2 (-1.5, -0.6)</td>
<td>-1.3 (-1.6, -0.6)</td>
<td>+0.2 (-0.4, 0.8)</td>
<td>-2.0 (-2.5, -1.1)</td>
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<td>Bone turnover markers</td>
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<td></td>
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<tr>
<td>uNTX (nMBCE/mmol), median (IQR)</td>
<td>41.5 (35.3, 57.9)</td>
<td>39.7 (28.3, 51.4)</td>
<td>—</td>
<td>51.6 (39.8, 71.6)</td>
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<tr>
<td>sCTX (ng/mL), median (IQR)</td>
<td>0.725 (0.58, 1.01)</td>
<td>0.686 (0.56, 0.99)</td>
<td>—</td>
<td>0.79 (0.74, 0.97)</td>
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<td>sBALP (µg/L), median (IQR)</td>
<td>15.3 (11.9, 18.1)</td>
<td>14.2 (10.8, 17.8)</td>
<td>—</td>
<td>18.9 (15.9, 22.3)</td>
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Abbreviations: IQR, interquartile range; BMI, body mass index.
ibandronate in postmenopausal women without breast cancer. This assumed that the common SD was 3.7 using a two-group $t$ test with a 0.05 two-sided significance level. To allow for a 10% dropout rate, 50 patients (25 in each group) were recruited to ensure adequate numbers at the end of the study. When the required 50 osteopenic patients were recruited, no further patients were recruited to the study. BMD changes from baseline at the LS and TH for the 1- and 2-y follow-up visits were normally distributed and thus expressed as percentages with 95% confidence intervals. Comparison between groups was done using the independent-samples $t$ test.

The bone biomarker data changes on study were also normally distributed and expressed as a mean percentage change from baseline. Comparisons at each time point were expressed graphically using 95% confidence intervals. Statistical analysis between the two groups was done using the independent-samples $t$ test. To evaluate the ability of bone marker changes at 3 mo to predict changes in BMD at 12 mo, an exploratory regression analysis was done using the Pearson's correlation coefficient. All statistical analysis was done using SPSS version 11.0, 2005.

Role of the funding source. This academic study was supported by unrestricted grants from Astra Zeneca and Roche, who also supplied the trial medications of anastrozole and ibandronate, respectively. Both companies were kept informed of the progress of the study but had no involvement in the analysis or interpretation of the results presented.

Results

Between December 2003 and October 2005, 131 postmenopausal, surgically treated breast cancer patients were recruited from oncology clinics in Leeds and Sheffield, United Kingdom. A total of 50 recruited patients were identified as having osteopenia at the time of the baseline scan. Sixty-eight of the remaining 81 patients had normal BMD and 13 already had osteoporosis before starting anastrozole.

The baseline characteristics are summarized in Table 1. Patients with normal BMD were on average younger and had a higher body mass index than the osteopenic and osteoporotic patients. Patients with osteoporosis were of similar age and body mass index as the osteopenic population; however, their average bone turnover marker levels were higher.

In the randomized population of women with osteopenia, the baseline characteristics were similar between the group allocated to ibandronate and those allocated to placebo.

Two patients, both receiving ibandronate, requested withdrawal from the study before the 1-year visit due to side effects from their anastrozole tablets (joint pains $n = 1$, atrophic vaginitis $n = 1$). In both these cases, no follow up BMD data were available.

Bone mineral density. At the LS, the mean percentage change in BMD in osteopenic patients treated with anastrozole plus ibandronate increased by +3.11% (range -3.8, +15.1) after 1 year and by +2.98% (range -8.9, +19.9) after 2 years. At the TH, BMD increased by +0.98% (range -4.1, +5.6) after 1 year and stabilized to +0.60% (-9.0, +6.9) after 2 years (see Fig. 2A and B).

In the anastrozole plus placebo group, mean declines in BMD were observed at 1 and 2 years both at the LS (-2.35% and -3.22%; range -16.0, +4.3, respectively) and TH (-2.27% and -3.90; range -12.3, +7.2 respectively; see Fig. 2A and B). The differences between the two treatment arms were statistically significant at both sites and at each time point ($P < 0.01$, independent-samples $t$ test).

After 2 years, five osteopenic patients receiving anastrozole plus placebo developed osteoporosis and were offered bisphosphonate treatment. One patient treated with anastrozole plus ibandronate who had a baseline $T$ score of -2.3 developed osteoporosis ($T$ score = -2.7) after 2 years. Six patients treated with ibandronate developed normal BMD ($T$ score >-1.0) compared with none in the placebo group (see Table 2).

Six patients who were osteopenic at baseline lost greater than 4% BMD at either their LS or TH following 2 years of treatment with ibandronate. In each of these cases, the bone loss occurred at only one of the measured sites (LS = 2, TH = 4).

Fig. 2. A, percentage change in lumbar spine BMD for patients treated with ibandronate and placebo (error bars, 95% CI). B, percentage change in hip BMD for patients treated with ibandronate and placebo (error bars, 95% CI).
Figure 3 shows the proportion of patients who lost or gained bone density in each of the randomized groups. Patients treated with ibandronate were more likely to achieve significant gains in LS and TH BMD compared with those treated with placebo.

In the group with normal BMD (T score >-1.0), the mean percentage change in LS and TH BMD was -4.79 (range -13.8, +4.5) and -3.72 (range -15.9, +1.3), respectively, after 2 years. For those patients with osteoporosis at baseline, receiving anastrozole plus ibandronate, BMD increased by +3.52 (range -4.9, +14.6) at the LS and by +2.49% (range -3.7, +8.1) at the TH.

**Bone turnover markers.** In patients receiving anastrozole plus placebo, significant increases in bone turnover markers were observed. The 12-month mean percentage change from baseline was +39.5%, +34.9%, and +37.0% for uNTX, sCTX, and sBALP, respectively (see Fig. 4A-C). Conversely, treatment with anastrozole plus ibandronate was associated with significant declines of the bone resorption markers (uNTX and sCTX) and also the bone formation marker (sBALP). The 12-month mean percentage change from baseline was -30.9%, -26.3%, and -22.8% for uNTX, sCTX, and sBALP, respectively. Differences between ibandronate- and placebo-treated patients were highly significant for each marker at 12 months (P < 0.001).

Bone turnover markers also provide an indirect assessment of treatment compliance. Seventy-four percent of those taking ibandronate had a decrease in NTX of >10%. This contrasts with only 4% of those taking placebo and in whom 77% had a >10% increase in NTX.

**Adverse events.** Typical anastrozole side effects were observed, particularly joint pains and flushes. The number of patients suffering joint pains was similar in each of the randomized groups (ibandronate = 6, placebo = 5). Upper gastrointestinal tract symptoms such as nausea and indigestion were experienced by 4 (16%) of those treated with ibandronate compared with none in those taking placebo. For three of the patients, the gastrointestinal tract symptoms were generally mild and limited to a few days following the ibandronate treatment. In one case, the patient developed prolonged indigestion and was unable to take the ibandronate after 12 months. Osteonecrosis of the jaw did not occur.

There were no fragility fractures reported in either group but two patients taking ibandronate (wrist = 1, hip = 1) and three taking placebo (wrist = 1, shoulder = 1, rib = 1) experienced a traumatic fracture.

Tablet compliance of the ibandronate was very good with more than 90% of study patients taking all of their monthly doses.

**Correlation between changes in bone turnover and BMD.** To determine if early changes in bone turnover markers could predict for future changes in BMD, a correlation analysis was done. Changes from baseline in bone turnover markers during the first 3 months were related to subsequent changes from baseline in BMD at 12 months. No significant correlations were observed for either the resorption or formation markers measured (data not shown).

**Discussion**

Following the encouraging results of trials of aromatase inhibitors in the adjuvant setting, increasing numbers of postmenopausal women are offered one of these agents in preference to tamoxifen as adjuvant endocrine therapy. Many of these women will be long-term survivors and are thus at risk from the long-term side effects of treatment such as osteoporosis and fracture. In both the ATAC trial, evaluating anastrozole, and the BIG1-98 trial, studying letrozole, an ~40% to 50% excess annual risk of fracture with the aromatase inhibitor compared with tamoxifen was observed (1, 3). Although tamoxifen has been shown to reduce the fracture rate in postmenopausal women (18), the magnitude of effect and the biochemical evidence of increased bone turnover in patients treated with an aromatase inhibitor (19) argues strongly for a direct adverse effect of these agents on bone health.

In this study, the bone loss observed in patients treated with anastrozole without bisphosphonate therapy was similar to that reported in the ATAC trial at ~2% to 3% per year. In the course of the first year, two women who were previously osteopenic lost >10% BMD and became osteoporotic, indicating that regular monitoring of these patients is essential.

The addition of oral ibandronate 150 mg monthly to anastrozole led to significant increases in both the BMD of

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**Table 2. Changes in BMD groupings following 2 years of ibandronate or placebo**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Normal BMD</th>
<th>Osteopenia</th>
<th>Osteoporosis</th>
<th>Withdrawals/no 1-y data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteopenia + ibandronate</td>
<td>25</td>
<td>6 (26%)</td>
<td>16 (70%)</td>
<td>1 (4%)</td>
<td>2</td>
</tr>
<tr>
<td>Osteopenia + placebo</td>
<td>25</td>
<td>0 (0%)</td>
<td>20 (80%)</td>
<td>5 (20%)</td>
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</tr>
</tbody>
</table>

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**Figure 3.** The percentage of patients who lost or gained LS and TH BMD in each of the randomized groups.
the LS and TH. The rate of bone turnover was suppressed below baseline values throughout the study period, indicating rapid and sufficient dosing and absorption with the same monthly oral schedule used in the treatment of PMO. In this small study, early changes in bone marker levels did not reliably predict for subsequent changes in BMD and are thus probably not of value in predicting individuals who will experience rapid loss of bone. They do, however, provide indirect evidence of treatment compliance.

Treatment with anastrozole alone led to significant increases in all bone turnover markers. Changes were higher than those observed in the ATAC trial (ref. 19; NTX +39.5% versus +15%), which may be explained by the higher baseline bone density in those recruited to the ATAC trial bone subprotocol (median LS T score -0.8 versus -1.2).

This is the first study to report 2-year data on the use of an oral bisphosphonate for the treatment of aromatase inhibitor–induced bone loss. Recently, a preliminary analysis of 12-month data from the SABRE study was presented, indicating that oral risedronate 35 mg weekly may also be an effective treatment in terms of BMD changes at 12 months (20). Zoledronic acid had also been shown to prevent aromatase inhibitor–induced bone loss. In the Z-FAST study (16), improvements in LS and TH BMD (+1.9% and +1.3%, respectively) were observed at 12 months following six monthly infusions of zoledronic acid (4 mg) in addition to treatment with the aromatase inhibitor letrozole, a dose intensity somewhat greater than the 5 mg/y used in the treatment of PMO. In this study, indirect comparisons suggest a similar increment in BMD with oral ibandronate to other bisphosphonates. Additionally, in the small number of patients with osteoporosis at baseline, oral ibandronate improved BMD in the majority (8 of 11) of patients. Treatment was well tolerated and as anticipated in a study with occasional oral bisphosphonate use, there were no episodes of osteonecrosis of the jaw. Guidance from the American Society of Bone and Mineral Research estimates the frequency of osteonecrosis of the jaw in patients taking oral bisphosphonates for osteoporosis at 1 in 10 to 100,000 cases (21).

There are a number of guidelines on the management of bone loss associated with the use of aromatase inhibitors published or in development. There is common agreement that bone protection with a bisphosphonate is required for patients with osteoporosis. Similarly emerging data from the ATAC (10) and IES studies (22) indicate that the bone loss is relatively predictable and, thus, for women with normal BMD before starting endocrine therapy, the risk of developing osteoporosis over 3 to 5 years on an aromatase inhibitor is very low and lifestyle advice, reassurance, and very limited, if any, follow-up measurements of BMD are all that is required. Controversy persists on the management of patients with osteopenia. Adequate intake of calcium and vitamin D, a healthy lifestyle, and regular (12-24 month) follow-up dual-energy X-ray absorptiometry scanning should be routine. However, the role of prophylactic bisphosphonates is uncertain. Several studies, including this one, indicate that bisphosphonates will prevent bone loss in this patient population.

Specific guidelines on how to investigate and treat cancer therapy–induced bone loss have recently been developed (23, 24). Our results suggest that monthly oral ibandronate is
an effective treatment and one of a range of bisphosphonate treatments that could be considered for women with low BMD receiving an aromatase inhibitor.

Disclosure of Potential Conflicts of Interest

D. Dodwell is a member of the AstraZeneca and Roche speakers’ bureau; R. Hannon received a research grant from AstraZeneca; R. Coleman received research support from AstraZeneca and Roche and is a member of the Roche speakers’ bureau.

References

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