Drug product:	Anastrozole 1 mg	**SYNOPSIS**	
Drug substance(s):	ZD1033 (anastrozole)		
Document No.:	1		
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A multicentre phase III/IV study, of the effects of risedronate sodium (ACTONEL™, 35 mg/week, oral) on bone, in postmenopausal women, with hormone-receptor-positive early breast cancer, treated with anastrozole (ARIMIDEX™, 1 mg/day oral) with either high-risk of fragility fracture (open-label, non-comparative stratum), or moderate-risk of fragility fracture (randomised, double-blind stratum), and of the effects of anastrozole (ARIMIDEX™, 1 mg/day oral) on bone, in postmenopausal women, with hormone-receptor-positive early breast cancer, and low-risk of fragility fracture (open-label, non-comparative stratum)

Study centre(s)

This study was conducted in Canada (5 centres), France (5 centres), Greece (3 centres), The Netherlands (4 centres), South Africa (4 centres), Spain (4 centres), United Kingdom (4 centres) and United States (9 centres).

Publications

The SABRE (Study of Anastrozole with the Bisphosphonate RisedronatE) study: the effects of risedronate on BMD and bone metabolism in postmenopausal women using anastrozole as adjuvant therapy for hormone receptor-positive early breast cancer – first results. Van Poznak C, Hannon RA, Clack G, Campone M, Mackey JR, Apffelstaedt J, et al on behalf of the SABRE investigators. Poster presented at the 29th Annual San Antonio Breast Cancer Symposium; 2006 December 14-17; Texas, USA.

First results of the SABRE (Study of Anastrozole with the Bisphosphonate RisedronatE) study: effects of risedronate on BMD and bone metabolism in postmenopausal women using anastrozole as adjuvant therapy for hormone receptor-positive early breast cancer. Van Poznak C, Hannon RA, Clack G, Campone M, Mackey JR, Apffelstaedt J, et al on behalf of the SABRE investigators. Poster presented at the 6th International Meeting on Cancer-Induced Bone Disease; 2006 December 10-14; San Antonio, Texas, USA.

Study dates		**Phase of development**
First patient, first visit	20 April 2004	Therapeutic confirmatory (III) /Therapeutic use (IV)*
Last patient, last visit	Not applicable; study ongoing.	

* This study is a post marketing commitment to the Food and Drug Administration of the United States (FDA) and the Therapeutic Products Directorate (Canada) following approval of anastrozole for use in treating postmenopausal women with hormone receptor-positive early breast cancer. This study is considered a Phase IV study in those participating countries where approval has been received. In those countries where approval is yet to be received (at the time of study start), the study is considered Phase III.

Objectives

The primary objectives of this study were:

- To assess the combined effects of anastrozole and risedronate sodium[1] on changes in bone mineral density (BMD) from baseline in postmenopausal women with hormone receptor-positive early breast cancer who have high risk[2] of fragility fracture.
- To assess the effects of risedronate when compared with placebo, on changes in BMD from baseline in postmenopausal women with hormone receptor-positive early breast cancer, treated with anastrozole, who have moderate risk of fragility fracture.
- To assess the effects of anastrozole alone on changes in BMD from baseline in postmenopausal women with hormone receptor-positive early breast cancer, who have low risk[2] of fragility fracture.

Secondary objectives of the study were:

- To assess the combined effects of anastrozole and risedronate on changes in levels of bone resorption and formation markers from baseline, in postmenopausal women with hormone receptor-positive early breast cancer who have high risk of fragility fracture.
- To assess the effects of risedronate compared with placebo on changes in levels of bone resorption and formation markers from baseline, in postmenopausal women with hormone receptor-positive early breast cancer, treated with anastrozole who have moderate risk of fragility fracture.
- To assess the effects of anastrozole on changes in levels of bone resorption and formation markers from baseline, in postmenopausal women with hormone receptor-positive early breast cancer at low risk of fragility fracture.
- To assess the safety and tolerability of risedronate when taken in combination with anastrozole in postmenopausal women with hormone receptor-positive early breast cancer who have either moderate or high risk of fragility fracture.
- To determine the change in low-density lipoprotein-cholesterol (LDL-C) relative to baseline after 12 months of treatment with anastrozole alone, and to explore other changes in lipid profiles relative to baseline at various time points after treatment with anastrozole alone, or anastrozole in combination with risedronate.

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[1] *Risedronate sodium is referred to as risedronate throughout this report.*
[2] *Throughout this report, 'high-risk' is used to denote a 'higher risk than the moderate-risk group' and 'low-risk' is used to denote a 'lower risk than the moderate-risk group'.*

Study design

This study was divided into 3 strata:

1. An open-label, non-comparative stratum to evaluate the effects of anastrozole (1 mg/day orally) plus risedronate (35 mg/week orally) on BMD and markers of bone resorption and formation in postmenopausal women with hormone receptor-positive early breast cancer, and high risk of fragility fracture.

2. A randomised, double-blind stratum, comparing the effects of anastrozole (1 mg/day orally) plus risedronate (35 mg/week orally) and anastrozole (1 mg/day orally) plus a matching risedronate placebo on BMD and markers of bone resorption and formation, in postmenopausal women with hormone receptor-positive early breast cancer, with moderate risk of fragility fracture.

3. An open-label, non-comparative stratum to evaluate the effects of anastrozole (1 mg/day orally), on BMD and markers of bone resorption and formation in postmenopausal women with hormone receptor-positive early breast cancer, with low risk of fragility fracture.

Target patient population and sample size

Postmenopausal women with hormone receptor-positive early breast cancer. The patients were assigned to 1 of 3 strata depending on their risk of fragility fracture. Patients considered to be high risk had a T-score < -2.0 in either the lumbar spine, or hip, or a personal history of fragility fracture. Low risk patients had a T-score in both the lumbar spine, and total hip, of -1.0 or higher, and no personal history of fragility fracture. Patients who had a T-score < -1.0 in either lumbar spine or hip (provided neither of these was less than –2.0), and with no personal history of a fragility fracture could choose, in conjunction with the investigator, to be assigned to the high-risk or moderate-risk strata dependent on several clinical criteria (advanced age, early menopause [< age 45 years], low body weight [< 127 lbs/58 kg], current smoking, and history of fragility fracture in a first-degree relative).

Allowing for a drop-out rate of 30%, it was planned to recruit a minimum of 33 patients into the high-risk stratum, a minimum of 166 patients into the moderate-risk stratum, and a minimum of 40 patients into the low-risk stratum to give the desired power of 90%, with a 2-sided significance level of 5% to detect a change in BMD of a magnitude previously observed on anastrozole treatment (high and low-risk strata), or to detect a difference of that magnitude between the randomised treatments (moderate-risk stratum). For the lipid analysis, 87 evaluable patients would guarantee that the study could detect a 6% difference in LDL-C from baseline with a power over 90%.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

In the high- and moderate-risk strata patients received:

Anastrozole (ARIMIDEX™) 1 mg once daily in oral tablet form, in combination with risedronate sodium (ACTONEL™) 35 mg once weekly (or placebo in moderate-risk stratum) in oral tablet form and 2 elemental calcium 500 mg/vitamin D 200 IU combination tablets per day orally.

In the low-risk stratum patient received:

Anastrozole 1 mg once daily in oral tablet form and 2 elemental calcium 500 mg/vitamin D 200 IU combination tablets per day orally.

No comparator was used for patients in high- and low-risk strata. The comparator for patients in moderate-risk stratum was placebo risedronate (matching the active product).

The formulation/ADM (Analytical Development Macclesfield) numbers of the treatments used in this study are shown in Table S1.

Table S1 Formulation/ADM numbers of study treatments

Formulation title	Formulation number	ADM number
Risedronate 35 mg tablets	F013138	33274E05, 20647E04
Placebo risedronate 35 mg tablets	F013139	33275B05, 20648B04
Calcichew D3 (calcium carbonate 1250 mg)	F013140	24159C04, 33298G05, 20043C04, 23627C04, 32453B05, 41200H06
Anastrozole 1 mg (sales)	AR04	BP832, BY087, CA872, CD657, CS825, DC295

Duration of treatment

Patients in all strata are to be treated and followed for a maximum of 2 years (24 months). This clinical study report (CSR) presents data for the 6 and 12-month analyses.

Criteria for evaluation (main variables)

Efficacy and pharmacodynamics

- Primary variable:
  - In all strata, the primary outcome variable was the change from baseline in lumbar spine (lumbar vertebra L1 – L4) BMD at 12 months.
- Secondary variables:
  - Change from baseline in total hip BMD at 12 and 24 months.
  - Change from baseline in lumbar spine (L1 – L4) BMD at 24 months.
  - Change from baseline in bone formation markers at 6 and 12 months.
  - Change from baseline in bone resorption markers at 6 and 12 months.
  - Change from baseline in LDL-C at 12 months.
  - Change from baseline in LDL-C at 3 and 6 months, and high-density lipoprotein-cholesterol (HDL-C), total cholesterol (TC) serum triglycerides (TG) and TC:HDL-C ratio at 3, 6, and 12 months.

Safety

Safety and tolerability for all patients was assessed at all visits through the collection of adverse events (AEs) and serious adverse events (SAEs).

Statistical methods

In the high-risk and low-risk strata, the differences between the baseline and 12-month post-baseline values were analysed using a paired t-test. In the moderate-risk stratum, an analysis of covariance (ANCOVA) was used to examine the change from baseline to 12 months post-baseline in BMD between the anastrozole in combination with risedronate group, and anastrozole in combination with placebo group in the lumbar spine of hip BMD. The model was fitted with the covariates of baseline BMD, time since last menstrual period and body mass index (BMI). The treatment received population was used for the primary analyses of BMD (primary analysis population [PAP]). These analyses were repeated using a secondary per protocol population (PP). The same approach was used for the analyses of bone formation and resorption markers. An analysis of markers of bone resorption and formation only was performed when all patients in the study had completed their 6-month visit. This 6-month analysis was considered the primary analysis for the bone marker variables. LDL-C, HDL-C, TC, TG and TC:HDL-C ratio were analysed independently of strata in patients who did not have elevated cholesterol at baseline, according to the ATP [Adult Treatment Panel] III criteria, more specifically those with TC < 6.2 mmol/L and LDL-C < 4.2 mmol/L, who did not receive lipid lowering medication at baseline, and who

received anastrozole or anastrozole+placebo (primary analysis population for lipids [PAPL]) or anastrozole+risedronate (secondary population for lipids [SP]). As a robustness check, lipid profile variables were also analyzed in all patients who received anastrozole alone or anastrozole+placebo (intent-to-treat [ITT] population), as well as in the per protocol population for lipids (PPL), based on the PAPL, but excluding major deviators and patients who started lipid lowering medications while on study. The difference between post-baseline and baseline values was calculated for each lipid variable. These differences were analysed using a paired t-test.

Patient population

The analysis sets and the number of patients in each analysis set are summarised in Table S2.

Table S2 12-month analysis sets

Population	n (%) patients			
	Stratum			
	Low	Moderate		High
	Anastrozole 1 mg	Anastrozole 1 mg+ placebo	Anastrozole 1 mg+ risedronate 35 mg	Anastrozole 1 mg+ risedronate 35 mg
Randomised	42 (100)	77 (100)	77 (100)	38 (100)
Safety population	42 (100)	77 (100)	77 (100)	38 (100)
BMD and bone markers				
PAP[a]	42 (100)	77 (100)	77 (100)	38 (100)
PP[b] (Visit 2, Baseline)	40 (95.2)	74 (96.1)	75 (97.4)	34 (89.5)
PP[b] Visit 3, Month 3)	39 (92.9)	67 (87.0)	73 (94.8)	34 (89.5)
PP[b] (Visit 4, Month 6)	33 (78.6)	57 (74.0)	68 (88.3)	34 (89.5)
PP[b] (Visit 5, Month 12)	30 (71.4)	50 (64.9)	58 (75.3)	31 (81.6)
	Anastrozole 1 mg Population		**Anastrozole 1 mg + risedronate 35 mg Population**	
Lipids				
ITT[c]	119		NA	
PAPL[d]	66		NA	
SP[e]	NA		65	
PPL[f] (12 months)	46		NA	

a All patients (high- or moderate-risk strata) who received both anastrozole and risedronate (active or placebo) and all patients (low-risk strata) who received anastrozole. The PAP was identical to the safety population.

b Based on the PAP but excluded any ineligible patients (those who did not satisfy all the inclusion/exclusion criteria at the time of randomisation) and major deviators starting at the timepoint at which the deviation occurred, categorised according to treatment received.

c All patients who received anastrozole alone or anastrozole+placebo.

d All patients who had received anastrozole alone (low- and moderate-risk strata) and had not received any cholesterol-lowering drugs within the previous 12 months; did not have elevated cholesterol at baseline, according to the Adult Treatment Panel III criteria; or a major protocol violation.

e All patients who received both anastrozole and risedronate (high- and moderate-risk strata).

f Based on the PAPL but excluded any major deviators.

ITT Intent-to-treat; NA Not applicable; PAP Primary analysis population; PAPL Primary analysis population for lipids; PP Per-protocol population; PPL Per-protocol population for lipids; SP Secondary analysis population for lipids.

The PAP for BMD and bone markers consisted of 234 patients (42 patients in the low-risk stratum, 77 patients in the moderate-risk/anastrozole+placebo group, 77 patients in the moderate-risk/anastrozole+risedronate group and 38 patients in the high-risk stratum).

There were 66 patients in the PAPL, 65 patients in the SP and 46 patients in the PPL.

The demographic characteristics of study patients are summarised in Table S3.

Table S3 Summary of demographic characteristics (PAP)

Demographic characteristic	Stratum				
	Low	Moderate			High
	Anastrozole 1 mg (N=42)	Anastrozole 1 mg+ placebo (N=77)	Anastrozole 1 mg+ risedronate 35 mg (N=77)	All (N=154)	Anastrozole 1 mg+ risedronate 35 mg (N=38)
Age (years)					
Mean (SD)	62.8 (8.16)	64.8 (8.01)	63.8 (7.81)	64.3 (7.90)	65.6 (9.93)
Range	50 to 83	51 to 88	49 to 83	49 to 88	45 to 91
Sex, n (%)					
Female	42 (100)	77 (100)	77 (100)	154 (100)	38 (100)
Race, n (%)					
Caucasian	38 (90.5)	69 (89.6)	70 (90.9)	139 (90.3)	36 (94.7)
Black	0	2 (2.6)	1 (1.3)	3 (1.9)	1 (2.6)
Oriental	1 (2.4)	0	2 (2.6)	2 (1.3)	0
Other	3 (7.1)	6 (7.8)	4 (5.2)	10 (6.5)	1 (2.6)
BMI (kg/m^2)[a, b]					
Mean (SD)	30.6 (6.70)	26.6 (4.11)[b]	28.7 (5.51)[b]	27.7 (4.96)	25.7 (5.27)
Range	19 to 46	19 to 42	19 to 48	19 to 48	19 to 44

a Weight in kg/(height in metres)^2.
b One patient in each treatment group of the moderate-risk stratum had missing BMI data.
BMI Body mass index; PAP Primary analysis population; SD Standard deviation.

The demographic characteristics were similar between the treatment groups. Patients in the PAP had a mean age of 64.2 years (range: 45 to 91 years). The majority (91%) of the patients were Caucasian.

There were some minor variations between treatment groups in baseline characteristics but these were not considered to impact the study data and were within the range of values expected for this study population.

Efficacy and pharmacodynamic results

Results for the analysis of lumbar spine BMD at 12 months for the high-risk, moderate-risk and low-risk strata are presented in Table S4, Table S5 and Table S6, respectively.

Table S4 Analysis of lumbar spine BMD (g/cm²) at 12 months in the high-risk stratum (PAP)

High-risk stratum					
N[a]	Baseline gmean	gmean 12 months	Estimated % change[b] (95% CI)	Time effect[c] (95% CI)	p-value
36	0.839	0.867	3.3611 (2.0465, 4.6927)	1.0336 (1.0205, 1.0469)	< 0.0001

a Patients with values at baseline and 12 month visit.
b 100*((time effect) - 1).
c Ratio of post baseline value/baseline value.
BMD Bone mineral density; CI Confidence interval; gmean Geometric mean; PAP Primary analysis population.

Table S5 Analysis of change in lumbar spine BMD (g/cm²) from baseline to 12 months in the moderate-risk stratum (PAP)

	Moderate-risk stratum				
	N[a]	glsmean[b]	Treatment ratio[c] (95% CI)	Estimated % change[d] (95% CI)	p-value[b]
Anastrozole+placebo	65	0.988		-1.2179 (-2.1856, -0.2406)	
Anastrozole+risedronate	73	1.012	1.0245 (1.0134, 1.0357)	1.2000 (0.2228, 2.1866)	< 0.0001

a Patients with values at baseline and 12 month visit.
b Covariance analysis.
c Anastrozole+risedronate/anastrozole+placebo.
d 100*(glsmean)-1).
BMD Bone mineral density; Confidence interval; glsmean Geometric least squares mean; PAP Primary analysis population.

Table S6 Analysis of lumbar spine BMD (g/cm²) at 12 months in the low-risk stratum (PAP)

Low-risk stratum					
N[a]	Baseline gmean	gmean 12 months	Estimated % change[b] (95% CI)	Time effect[c] (95% CI)	p-value
35	1.147	1.140	-0.6174 (-1.9314, 0.7143)	0.9938 (0.9807, 10071)	0.3511

a Patients with values at baseline and 12 month visit.
b 100*((time effect)-1).
c Ratio of post baseline value/baseline value.
BMD Bone mineral density; CI Confidence interval; gmean Geometric mean; PAP Primary analysis population.

In postmenopausal breast cancer patients with a high risk of fragility fracture, treatment with anastrozole+risedronate for 12 months was associated with a statistically significant increase from baseline in lumbar spine BMD (estimated percentage change 3.36%; 95% confidence interval [CI]: 2.05, 4.69; p< 0.0001). In postmenopausal breast cancer patients with a moderate risk of fragility fracture, treatment with anastrozole+risedronate resulted in a statistically significant increase in lumbar spine BMD at 12 months compared with anastrozole+placebo treatment (estimated percentage change 1.20% versus –1.22%; treatment ratio 1.02; 95% CI: 1.01, 1.04; p< 0.0001). In postmenopausal breast cancer patients with a low risk of fragility fracture, treatment with anastrozole monotherapy was associated with no statistically significant change in lumbar spine BMD at 12 months (estimated percentage change -0.62%; 95% CI: -1.93, 0.71; p=0.3511). These findings were mirrored in the secondary efficacy variable of change from baseline in total hip BMD at 12 months.

Bone markers

In postmenopausal breast cancer patients with a high risk of fragility fracture, treatment with anastrozole+risedronate for 12 months resulted in a reduction in bone turnover compared with baseline as evidenced by a statistically significant decrease in markers of bone formation (serum procollagen Type I amino terminal propeptide [PINP] and bone alkaline phosphatase [ALP]) and resorption (serum C terminal crosslinking telopeptide of Type I collagen [sCTX]) at 6 and 12 months. In postmenopausal breast cancer patients with a moderate risk of fragility fracture, compared with the anastrozole+placebo group, treatment with anastrozole+risedronate resulted in a decrease in bone turnover as evidenced by a statistically significant decrease in markers of bone formation and resorption at 6 and 12 months. In postmenopausal breast cancer patients with a low risk of fragility fracture, treatment with anastrozole monotherapy for 12 months was associated with a statistically significant increase in sCTX and ALP and no statistically significant change in PINP. At 6 months, there were no statistically significant changes in PINP, ALP or sCTX.

Lipids

In the PAPL (anastrozole) and SP (anastrozole+risedronate), there was no statistically significant change in LDL-C from baseline to 12 months. In the PAPL, there was a

statistically significant increase in HDL-C from baseline to 12 months. In the SP, there was no statistically significant change in HDL-C. In the PAPL and SP, there was no statistically significant difference in TC or serum TG at 12 months compared with baseline. Analysis of the lipid endpoints in the ITT population supported the primary analysis. The mean TC:HDL-C ratio decreased from baseline to 12 months in both the PAPL and SP. In the PAPL, for patients with borderline high LDL-C at baseline, there was a trend for a shift to a better ATP III category, i.e. patients tended to have near optimal or optimal LDL-C at 12 months, although this was not formally analysed.

Safety results:

Table S7 summarises AEs in each category.

Table S7 Number (%) of patients who had an adverse event in any category (safety population)

	Number (%) of patients who had an adverse event in each category[a]			
	Strata			
	Low	**Moderate**		**High**
	Anastrozole 1 mg (N=42)	**Anastrozole 1 mg+ placebo (N=77)**	**Anastrozole 1 mg+ risedronate 35 mg (N=77)**	**Anastrozole 1 mg+ risedronate 35 mg (N=38)**
At least one AE	38 (90.5)	66 (85.7)	68 (88.3)	33 (86.8)
AE leading to discontinuation	1 (2.4)	6 (7.8)	2 (2.6)	1 (2.6)
AEs related to anastrozole only	24 (57.1)	39 (50.6)	44 (57.1)	18 (47.4)
AEs related to risedronate only[b]	0	9 (11.7)	8 (10.4)	7 (18.4)
AEs related to both anastrozole and risedronate[c]	0	11 (14.3)	6 (7.8)	2 (5.3)
AEs related to Vitamin D/calcium supplement	3 (7.1)	8 (10.4)	12 (15.6)	4 (10.5)
SAEs	4 (9.5)	4 (5.2)	4 (5.2)	3 (7.9)
SAEs leading to discontinuation	1 (2.4)	0	0	0
SAEs related to anastrozole only	0	1 (1.3)	0	0

Table S7 Number (%) of patients who had an adverse event in any category (safety population)

	Number (%) of patients who had an adverse event in each category[a]			
	Strata			
	Low	Moderate		High
	Anastrozole 1 mg (N=42)	Anastrozole 1 mg+ placebo (N=77)	Anastrozole 1 mg+ risedronate 35 mg (N=77)	Anastrozole 1 mg+ risedronate 35 mg (N=38)
SAEs related to risedronate only[b]	0	0	1 (1.3)	0
SAEs related to both anastrozole and risedronate[c]	0	0	0	1 (2.6)
AEs related to Vitamin D/calcium supplement	0	0	0	0
Deaths	1 (2.4)	0	0	0
AEs leading to death	1 (2.4)	0	0	0

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories. Only treatment-emergent AEs are presented.
b AEs/SAEs related to 'risedronate only' also include those related to placebo.
c AEs/SAEs related to 'both anastrozole and risedronate' also include those related to placebo.
AE Adverse event; SAE Serious adverse event.

In the low-risk stratum, 90.5% of the patients reported at least 1 AE during the study. A total of 57.1% of patients had AEs that were considered to be related to treatment with anastrozole. In 1 patient, an AE of cardiac failure became serious and the patient died 1 day after her last dose of anastrozole. This event was not considered by the investigator to be related to treatment. A further 3 patients had SAEs in the low-risk stratum.

In the moderate-risk stratum, slightly more patients had at least 1 AE in the anastrozole+risedronate compared with the anastrozole+placebo group. However, there were a higher percentage of patients with AEs leading to permanent discontinuation in the anastrozole+placebo group (7.8%) compared with the anastrozole+risedronate group (2.6%). Four patients in each group had serious AEs, none of which led to permanent treatment discontinuation.

In the high-risk stratum, 86.8% of patients had at least 1 AE during the study. One patient had an AE leading to permanent treatment discontinuation. There were 3 patients with SAEs.

Overall, the addition of risedronate treatment to anastrozole did not result in an increase in reports of AEs, AEs leading to discontinuation, SAEs or SAEs leading to discontinuation.

Overall, in the study there were very few reports of SAEs and only 1 SAE leading to permanent treatment discontinuation was reported.

Table S8 presents the most common AEs, as summarised by preferred term and treatment group.

Table S8 Number (%) of patients with the most commonly reported adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety population)

MedDRA preferred term	n (%) patients			
	Stratum			
	Low	Moderate		High
	Anastrozole 1 mg (N=42)	Anastrozole 1 mg+ placebo (N=77)	Anastrozole 1 mg+ risedronate 35 mg (N=77)	Anastrozole 1 mg+ risedronate 35 mg (N=38)
At least one AE	38 (90.5)	66 (85.7)	68 (88.3)	33 (86.8)
Arthralgia	11 (26.2)	16 (20.8)	21 (27.3)	10 (26.3)
Hot flush	8 (19.0)	22 (28.6)	20 (26.0)	4 (10.5)
Fatigue	4 (9.5)	8 (10.4)	12 (15.6)	2 (5.3)
Nausea	2 (4.8)	6 (7.8)	9 (11.7)	6 (15.8)
Asthenia	2 (4.8)	6 (7.8)	4 (5.2)	8 (21.1)
Myalgia	4 (9.5)	4 (5.2)	3 (3.9)	7 (18.4)
Headache	1 (2.4)	8 (10.4)	7 (9.1)	0
Depression	5 (11.9)	5 (6.5)	4 (5.2)	2 (5.3)
Cough	6 (14.3)	1 (1.3)	7 (9.1)	1 (2.6)
Insomnia	1 (2.4)	6 (7.8)	5 (6.5)	3 (7.9)
Constipation	2 (4.8)	5 (6.5)	4 (5.2)	3 (7.9)
Osteoarthritis	1 (2.4)	4 (5.2)	4 (5.2)	4 (10.5)
Bone pain	3 (7.1)	5 (6.5)	4 (5.2)	0
Back pain	1 (2.4)	4 (5.2)	4 (5.2)	2 (5.3)
Diarrhoea	2 (4.8)	4 (5.2)	4 (5.2)	1 (2.6)
Pain in extremity	1 (2.4)	2 (2.6)	5 (6.5)	2 (5.3)

Table S8 Number (%) of patients with the most commonly reported adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety population)

MedDRA preferred term	n (%) patients			
	Stratum			
	Low	Moderate		High
	Anastrozole 1 mg (N=42)	Anastrozole 1 mg+ placebo (N=77)	Anastrozole 1 mg+ risedronate 35 mg (N=77)	Anastrozole 1 mg+ risedronate 35 mg (N=38)
Lymphoedema	3 (7.1)	1 (1.3)	4 (5.2)	1 (2.6)
Musculoskeletal pain	2 (4.8)	3 (3.9)	2 (2.6)	2 (5.3)
Breast pain	0	1 (1.3)	5 (6.5)	2 (5.3)
Nasopharyngitis	0	3 (3.9)	2 (2.6)	3 (7.9)
Vulvovaginal dryness	1 (2.4)	1 (1.3)	5 (6.5)	1 (2.6)
Alopecia	0	2 (2.6)	4 (5.2)	1 (2.6)
Vomiting	1 (2.4)	1 (1.3)	2 (2.6)	2 (5.3)
Bronchitis	0	2 (2.6)	0	3 (7.9)
Cystitis	1 (2.4)	0	4 (5.2)	0
Dizziness	0	0	0	5 (13.2)
Hypoaesthesia	0	3 (3.9)	0	2 (5.3)
Rash	0	4 (5.2)	1 (1.3)	0
Abdominal distension	1 (2.4)	0	1 (1.3)	2 (5.3)
Gastritis	1 (2.4)	0	1 (1.3)	2 (5.3)
Urinary tract infection	0	1 (1.3)	1 (1.3)	2 (5.3)
Dental caries	0	0	0	2 (5.3)

Data derived from Table 11.3.2.2, Section 11.3
This table uses a cut-off of 5% in any treatment arm.
Only treatment-emergent AEs are presented.
AE Adverse event; MedDRA Medical Dictionary for Regulatory Activities.

Overall, arthralgia was the most frequently reported AE followed by hot flush and fatigue. There were some differences in the incidence of the most commonly reported AEs between the treatment groups.

Looking at the moderate-risk stratum, the most commonly reported AEs had a similar incidence in each treatment group, apart from arthralgia, fatigue and cough which were reported in a higher percentage of patients in the anastrozole+risedronate group compared with the anastrozole+placebo group.

Date of the report

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