Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Anastrozole 1mg Film-coated Tablets

anastrozole

PL 20075/0075

Accord Healthcare Limited

LAY SUMMARY
Anastrozole 1mg Film-coated Tablets
anastrozole

This is a summary of the Public Assessment Report (PAR) for Anastrozole 1mg Film-coated Tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Anastrozole Tablets in this lay summary for ease of reading.

For practical information about using Anastrozole Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Anastrozole Tablets and what are they used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Arimidex 1mg tablets.

Anastrozole Tablets is used to treat breast cancer in women who have gone through the menopause and as a preventative treatment in postmenopausal women at moderate or high risk of breast cancer.

How do Anastrozole Tablets work?
Anastrozole Tablets contain a substance called anastrozole. This belongs to a group of medicines called aromatase inhibitors. Anastrozole Tablets work by cutting down the amount of the hormone called oestrogen that the body makes. It does this by blocking a natural substance (an enzyme) in the body called ‘aromatase’.

How are Anastrozole Tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The recommended dose is one tablet once a day.

Patients should try to take their tablet at the same time each day and they should swallow the tablet whole with a drink of water. It does not matter if Anastrozole tablets is taken before, with or after food.

Patients should keep taking Anastrozole tablets for as long as their doctor or pharmacist tells them to. It is a long-term treatment and the patient may need to take it for several years.

<u>Use in children and adolescents</u>
Anastrozole tablets should not be given to children and adolescents.

For further information on how Anastrozole Tablets is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Anastrozole Tablets have been shown in studies?
Because Anastrozole Tablets is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

The new indication of primary prevention of breast cancer was supported by evidence based on the IBIS-II study, an international, randomised double-blind, placebo-controlled trial, which showed fewer women developed breast cancer in the anastrozole group compared to the placebo group.

What are the possible side effects of Anastrozole Tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Anastrozole Tablets (which may affect more than 1 in 10 people) are-

• Hot flushes
• Feeling weak
• Pain or stiffness in the joints
• Inflammation of the joints (arthritis)
• Skin rash
• Feeling sick (nausea)
• Headache
• Bone loss (osteoporosis)
• Depression.

Why were Anastrozole Tablets approved?
It was concluded that, Anastrozole Tablets have been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use for the treatment of breast cancer in women who have gone through the menopause.

It was concluded that Anastrozole Tablets have been shown to be effective in the-

- Treatment of hormone receptor-positive advanced breast cancer in postmenopausal women. Efficacy has not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen.
- Adjuvant treatment of hormone receptor positive early invasive breast cancer in postmenopausal women.

- Adjuvant treatment of hormone receptor positive early invasive breast cancer in postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.
- Primary prevention of breast cancer in postmenopausal women at moderate or high risk.

Furthermore, the side effects observed with use of this product are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine/these medicines can be approved for use.

What measures are being taken to ensure the safe and effective use of Anastrozole Tablets?

As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Anastrozole Tablets. The RMP details the important risks of Anastrozole Tablets, how these risks can be minimised, any uncertainties about Anastrozole Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Anastrozole Tablets:

Important identified risks	• Osteoporosis
Important potential risks	• Rheumatoid arthritis
Missing information	• None

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Anastrozole Tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Anastrozole Tablets

A marketing authorisation for Anastrozole Tablets was granted in the United Kingdom (UK) on 21 October 2008.

The full PAR for Anastrozole Tablets follows this summary.

This summary was last updated in December 2023.

TABLE OF CONTENTS

Please note, the below scientific discussion consists of the original assessment of this Marketing Authorisation. The original assessment is followed by a table of key post approval changes and relevant (non-safety related variation) annexes. The PAR is configured in this manner to improve the accuracy of this Public Assessment Report and to provide a better understanding of authorisation's lifecycle.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Anastrozole 1 mg film-coated tablets, in the treatment of breast cancer in post menopausal women, is approvable.

This abridged decentralised application concerns a generic version of anastrozole submitted under Article 10.1. The originator product is Arimidex 1mg tablets authorised to AstraZeneca UK Ltd since 1995. The legal basis is satisfactory.

With the UK as the Reference Member State in this Decentralised Procedure, Accord Healthcare Limited is applying for the Marketing Authorisations for Anastrozole 1mg tablets in CY, CZ, EE, EL, ES, LT, LV, MT, PL, PT, RO, SI and SK.

Anastrozole belongs to the hormone antagonists group. Anastrozole is a non-steroidal aromatase inhibitor and acts by predominantly by blocking the conversion of androgens to oestrogen in the peripheral tissues and is indicated for use in adjuvant treatment of oestrogen receptor-positive breast cancer in postmenopausal women.

No new preclinical or clinical studies were conducted and none are required for an application of this type. This application for a generic product refers to Armidex 1mg Tablets, which has been licensed within the EEA for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The applicant has submitted a phase I clinical bioequivalence study and it has been conducted under GCP guidelines.

II QUALITY ASPECTS

II.1 Introduction

The active substance is anastrozole. Each film-coated tablet contains 1mg of anastrozole.
The other ingredients are-
Core tablet: lactose monohydrate, povidone K30, sodium starch glycolate (type A) and magnesium stearate.
Film-coating: titanium dioxide (E171), macrogol 300 and hypromellose E-5.

All excipients used comply with their respective European Pharmacopoeia monograph.

The finished product is packaged in PVC/PVDC/Aluminium blisters in packs of 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100 or 300 tablets.

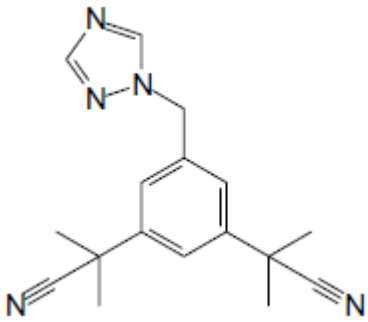
Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

Drug Substance

Nomenclature and structure



Description:	White or almost white powder
Solubility:	Moderately soluble in water, Freely soluble in methanol, acetone, ethanol and THF and very soluble in acetonitrile
Chemical name:	1,3-benzenediacetonitrile, α, α, α', α'-tetramethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl) 2-[3-(1-cyano-1-methylethyl)-5-(1*H*,1,2,4-triazol-1-ylmethyl)phenyl]-2-methylpropanenitrile
Molecular formula:	$C_{17}H_{19}N_5$
Melting range:	81-84ºC

The active substance used in the manufacture of the final product is in compliance with GMP.

A letter of access to the new EDMF is provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active anastrozole is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data has been provided.

II.3 DRUG PRODUCT

Pharmaceutical development

The objective of the pharmaceutical development programme was to produce a product containing anastrozole 1mg film-coated tablets are tolerable and which could be considered as generic product to the originator product Arimidex 1mg Tablets.

The only excipients used that contain material of animal or human origin are lactose anhydrous and magnesium stearate. The applicant has provided a declaration that the milk used in the production of lactose anhydrous is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

Dissolution and impurity profiles

Dissolution and impurity profiles for the drug product were found to be similar to that for the reference product.

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches. The results are satisfactory. Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years with no storage condition has been set. These are acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

No new preclinical data have been supplied with this application and none are required for applications of this type.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology

No new toxicology data were provided, and none were required for this application.

III.5 Discussion on the non-clinical aspects

The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

This is a decentralised procedure submitted under article 10 (1) of Directive 2001/83/EC (as amended) for a known active substance. The UK is the reference member state (RMS) with a procedure number UK/H/1153/01/DC. The Concerned Member States (CMS) are CY, CZ, EE, EL, ES, LT, LV, MT, PL, PT, RO, SI and SK.

The proposed product Anastrozole 1 mg Tablet is claiming to be a generic of the brand leader Arimidex tablets 1 mg (AstraZeneca GmbH) (PL 17901/0002 - 0048). The active substance anastrozole, is a reversible (Type II), nonsteroidal aromatase inhibitor. The aromatase enzyme is involved in the production of oestrogen. In postmenopausal women the aromatase enzyme converts the sex hormones androstenedione and testosterone, into oestrogen. Anastrozole prevents this conversion by blocking the action of the aromatase enzyme, thus causing oestrogen levels in the body to fall. The original product is listed as Arimidex 1 mg tablet which was licensed in August 2005 in the UK.

IV. 2 Pharmacokinetics

The applicant has submitted one bioequivalence study comparing the bioavailability between Anastrozole 1 mg Tablets and the reference product Arimidex® 1 mg Tablets after a single dose in healthy subjects.

Project 002-06

The phase I bioequivalence study took place at Lambda Therapeutic Research Ltd, Ahmedabad, Gujarat, India. The study was conducted in line with GCP guidelines.

Study design

This was an open label, single dose, randomized, two-way, crossover study designated to evaluate the comparative bioavailability of two formulations of anastrozole 1 mg tablets administered to healthy male subjects.

Study drugs (one tablet 1 mg) were administered orally after an overnight fast of at least 10 hours with 240 ml of water. The washout period was 28 days. Blood samples were collected prior to drug administration and up to 288 hours post dose administration.

Test Anastrozole 1 mg film coated tablets
Reference Arimidex 1 mg film-coated Tablets

29 healthy male adults were enrolled in the trial. 28 subjects were dosed in period I. 26 subjects completed the study and plasma samples from these 26 volunteers were analysed.

Determination of anastrozole plasma concentrations was performed using a validated LC/MS/MS. Analysts were blinded of the sequence of administration of the drugs.

Pharmacokinetic Variables

T_{max}, C_{max}, $T_{1/2}$, AUC $_{(0-t)}$, AUC $_{(0-\infty)}$, AUCextrap.(%), Kel, λz.

Descriptive statistics were calculated for the PK parameters. Analysis of variance (ANOVA) was carried out on the log-transformed AUC0-t and Cmax. Ratios of the geometric means of the test product versus reference for AUC and Cmax were calculated together with the 90% confidence intervals of the ratios.

Results

The results are shown in tables A and B.

Table-A: Descriptive Statistics of Formulation Means for Anastrazole (n=26)

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Reference Product A	Test Product B
*T_{max} (h)	2.500	2.500
C_{max} (ng/mL)	15.356 ± 2.7862	15.915 ± 2.8639
AUC_{0-t} (ng.h/mL)	672.440 ± 214.2066	688.165 ± 213.7105
$AUC_{0-\infty}$ (ng.h/mL)	699.991 ± 221.8860 #	710.456 ± 217.9124
λ_x (1/h)	0.0199 ± 0.00542 #	0.0193 ± 0.00421
t½ (h)	37.373 ± 10.3561 #	37.635±8.3545
AUC_% Extrap_obs (%)	4.149 ± 2.2159 #	3.285 ± 1.3501

*Note: Median Value

Table-B: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Anastrazole (n=26)

Parameters (Units)	Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	Reference Product A	Test Product B	Ratio (B/A)%	
C_{max} (ng/mL)	15.126	15.660	103.5%	99.66-107.56%
AUC_{0-t} (ng.h/mL)	641.059	657.124	102.5%	98.88-106.27%
$AUC_{0-\infty}$ (ng.h/mL)	668.108 #	679.507	101.7%	98.01-105.54%

n=25: Descriptive statistics of (i.e. AUC_{0-inf}, λ_z, AUC_% Extrap_Obs) was computed and reported for subjects whose extrapolation area was found to be <20%.

Safety results showed no cause of concern.

Pharmacokinetic conclusion

Based on the submitted bioequivalence study the test Anastrozole 1 mg tablet is considered bioequivalent with the reference Arimidex® 1 mg tablet.

IV.3 Pharmacodynamics

No new data have been submitted and none are required. Anastrozole is a well-known potent and selective non-steroidal aromatase inhibitor that reduces the levels of circulating estradiol. This effect has been shown to be beneficial in post-menopausal women with breast cancer.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required for this application.

IV.5 Clinical safety

No new safety data have been submitted and none are required for this application.

IV.6 Discussion on the clinical aspects

The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The bioequivalence study has shown that the applicant’s product is bioequivalent to the reference product. The benefit risk assessment is considered positive and approval is recommended.

Conclusion

The proposed product has been shown to be a generic product of the reference product and has met the requirements with respect to qualitative and quantitative content of the active substance. Similar dissolution profiles have been demonstrated for the proposed and reference products. It is recommended that Marketing Authorisation should be granted for this application.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N
II	**Repurposing project to add indication 'Primary prevention of breast cancer in postmenopausal women at moderate or high risk'. Supported by IBIS-II study.**	**SmPC, PIL**	**06/11/2023**	**Grant**	**Y (Annex 1)**

Annex 1

Reference: PL 20075/0075 - 0057
Product: Anastrozole 1mg Film-coated Tablets

Type of Procedure: National

Submission category: Type II Variation

Reason
Repurposing project to add indication 'Primary prevention of breast cancer in postmenopausal women at moderate or high risk'. Supported by IBIS-II study. Updates to SmPC sections 4.1, 4.2, 4.4, 4.8, and 5.1. Consequential updates to the PIL and RMP.

Supporting evidence
The MAH has submitted an updated SmPC, PIL and RMP in support of the application.

This submission is largely based on publications on the IBIS-II study, an international, double-blind, randomised placebo-controlled trial of anastrozole for prevention in postmenopausal women at increased risk of developing breast cancer.

Cuzick J, Sestak I, Forbes JF, *et al*. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): An international, double-blind, randomised placebo-controlled trial. *Lancet* 2014; 383(9922): 1041–1048.

Cuzick J, Sestak I, Forbes JF, *et al*. Use of anastrozole for breast cancer prevention (IBIS-II): Long-term results of a randomised controlled trial. *Lancet* 2020; 395(10218): 117–122.

Sestak I, Singh S, Cuzick J, *et al*. Changes in bone mineral density at 3 years in postmenopausal women receiving anastrozole and risedronate in the IBIS-II bone substudy: An international, double-blind, randomised, placebo-controlled trial. *Lancet Oncol* 2014; 15(13): 1460–1468.

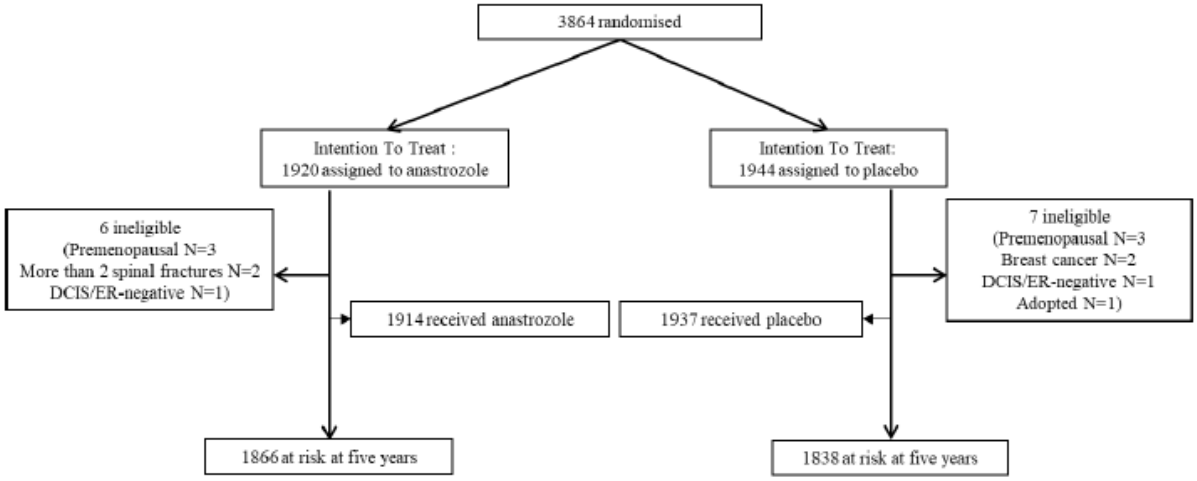
ISRCTN Registry. ISRCTN31488319 Anastrozole versus placebo in post-menopausal women at increased risk of breast cancer. Available at https://www.isrctn.com/ISRCTN31488319 [Accessed September 2022].

Evaluation

IBIS-II study

Recruitment period: between 02 Feb 2003 and 31 Jan 2012

CONSORT diagram:



13 women were ineligible after randomisation and were excluded from a secondary per-protocol analysis.

Inclusion criteria:

- postmenopausal women (bilateral oophorectomy; aged 60 years or older; less than 60 years with amenorrhoea for at least 12 months; less than 60 years with concentration of follicle stimulating hormone of greater than 30 IU/L)
- women aged 45–60 years who had a relative risk of breast cancer that was at least two times higher than in the general population
- women aged 40–44 years who had a risk that was four times higher
- women aged 60–70 years who had a risk that was at least 1·5 times higher
- women who did not meet other eligibility criteria were included if the Tyrer-Cuzick model indicated a 10-year risk of breast cancer of more than 5%

Exclusion criteria:

- premenopausal status
- any previous diagnosis of breast cancer (except for oestrogen receptor-positive ductal carcinoma in situ diagnosed less than 6 months previously and treated by mastectomy)
- any invasive cancer in the previous 5 years (except for non-melanoma skin cancer or cervical cancer)
- present or previous use of selective oestrogen receptor modulators for more than 6 months (unless as part of IBIS-I and treatment was completed at least 5 years before study entry)
- intention to continue hormone replacement therapy
- prophylactic mastectomy
- evidence of severe osteoporosis (T score <–4 or more than two vertebral fractures)
- life expectancy of fewer than 10 years
- psychologically or physiologically unfit for the study
- history of gluten or lactose intolerance, or both

Treatment: Women received 1 mg oral anastrozole or matching placebo every day for 5 years

Primary endpoint:
- histologically confirmed breast cancer (either invasive cancers or non-invasive [ductal carcinoma in situ])

Secondary endpoints:
- oestrogen-receptor-positive breast cancer
- breast cancer mortality
- other cancers
- cardiovascular disease
- fractures
- other adverse events
- deaths not due to breast cancer.

Clinic visits:
Baseline, 6 months, and 12 months, and then annually until the 5-year follow-up point. Follow-up after 5 years varied and consisted of a mixture of clinic visits, annual questionnaires, and also record linkage systems in the UK.

Investigations:
Mammogram: at baseline then at least every 2 years
DEXA scan and 2 lateral spinal x-rays: at baseline

Sample size:
Initial power calculations were based on a breast cancer incidence of 6 cases per 1000 women per year, and a compliance-adjusted reduction in breast cancer incidence of 50% for the anastrozole group. Predicated on these assumptions a sample size of 4000 women was initially targeted. However, initial figures showed a higher rate of breast cancer than predicted of 6.6 cases per 1000 women per year. When accounting for the assumed 50% reduction in the anastrozole group, this translated to a rate of 9 cases per 1000 women per year. This led to a reduction in the target sample size to 3500 women. Using this sample size and after 5 years median follow-up, it was expected that 78 breast cancer cases in the placebo group and 39 in the anastrozole group would be observed, providing statistical power in excess of 90% at a 5% significance level. Power to detect a difference between treatments for mortality was expected to be marginal at 10 years.

Randomisation and blinding:
Consenting eligible women were randomly assigned (1:1) to either anastrozole or matching placebo daily for 5 years. Randomisation was stratified by country and was done with randomly chosen randomisation blocks (size six, eight, or ten) to maintain balance. All participants and medical personnel were blinded to treatment allocation, which was only held by the central study statistician. Unblinding was only permitted if the participant developed breast cancer, when a clinician considered there to be valid medical or safety reasons, or the participant requested unblinding.

Statistical analysis:
The first major statistical analysis was planned for when at least 117 events (breast cancer cases) had occurred, and a median follow-up of 5 years reached. All analyses for all endpoints included all randomised women and were performed using the ‘intention-to-treat’ group. Safety data were summarised and listed by treatment allocated, with women who did

not start allocated treatment excluded. Women who did not develop breast cancer were right-censored at the date of their last visit.

This trial had the intent that no women should withdraw from the schedule of assessments and follow-up should be for 10 years after randomisation. However, women were able to stop treatment for the following reasons: development of breast cancer; adverse event; investigators recommendation. All who withdrew from the trial were included in trial listings and their reason for withdrawal and duration of trial treatment were recorded.

For all statistical analyses the nominal significance level was 5% (0.05) for a two-sided test. The log-rank test was used for the primary analysis to provide a basic comparison of treatment groups without adjusting for potential prognostic factors. This analysis was conducted using STATA (StataCorp; College Station, Texas), using the command "sts test varname, logrank" with the only variable included being randomised treatment. To allow an estimated hazard ratio (HR), associated confidence limits, and a p-value, the Cox proportional hazards model was used. The Cox proportional hazard models were fitted using the STATA "sts cox" command. The baseline covariates included in the models were: hormone replacement therapy (HRT) use; age; and body mass index (BMI). Results were to be presented as HRs with associated 2-sided 95% Confidence Intervals (CI) and p-values. For secondary endpoints (ER+ breast cancer and breast cancer mortality), Cox proportional hazards models were also used, following the same methodology and covariates as above.

An exploratory analysis on proportional hazards assumption was conducted. The assumptions of proportional hazards were assessed for each covariate by plotting the log {-log(survivor function)} against log(time). In addition, the assumption of proportionality for each covariate was investigated with time-dependent explanatory variables to allow for an increasing (decreasing) trend in the hazard ratio over time. If the p-value from the Wald chi-squared statistic for a time dependent variable was less than 5%, there was evidence of a departure from the model assumptions.

Adverse events were classified using MedRA terminology and tabulated for each treatment. Adverse event incidence rates were summarised by system organ class, preferred term, and severity of the adverse event (for pre-defined adverse events only). Pre-defined adverse events were: hot flushes/night sweats; vaginal changes; irregular vaginal bleeding; eye disease/cataracts; and osteoporosis/fractures. Each woman was counted only once within a system organ class or a preferred term by using the adverse events with the highest severity within each category. The incidence of each of the pre-defined adverse events were tabulated and formal statistical analysis was performed using logistic regression with only treatment group as a factor (STATA "logistic" command). For each treatment comparison, results from each test were presented as Odds Ratios (ORs), with associated 95% CI and p-value.

A further analysis was planned to take place around 5 years after the last report, and this analysis was provided 6 years after that report. The decision to analyse the data was made without looking at the results beforehand.

***Baseline characteristics*:**

	Anastrozole group (n=1920)	Placebo group (n=1944)
Age (years)	59·5 (55·0–63·5)	59·4 (55·1–63·3)
Age at menarche (years)	13·0 (1·2–14·0)	13·0 (12·0–14·0)
Parous	1601 (83%)	1637 (84%)
Age at first child birth (years)	24·0 (21·0–27·0)	24·0 (21·0–27·0)
Age at menopause (years)	50·0 (45·0–52·0)	49·0 (45·0–52·0)
Height (cm)	162·0 (158·0–166·0)	162·2 (158·0–167·0)
Weight (kg)	71·8 (64·0–82·2)	72·1 (64·0–83·5)
Body-mass index (kg/m²)		
<25	581 (30%)	568 (29%)
25–30	699 (36%)	732 (38%)
>30	640 (33%)	644 (33%)
Previous use of hormone replacement therapy	893 (47%)	910 (47%)
Use of hormone replacement therapy within previous 12 months	128 (7%)	152 (8%)
Hysterectomy	631 (33%)	656 (34%)
Two or more first-degree or second-degree relatives with breast or ovarian cancer	956 (50%)	938 (48%)
One first-degree relative with breast cancer at age 50 years or younger	675 (35%)	653 (34%)
One first-degree relative with bilateral breast cancer	164 (9%)	141 (7%)
Lobular carcinoma in situ or atypical hyperplasia	154 (8%)	190 (10%)
Oestrogen-receptor-positive ductal carcinoma in situ treated by mastectomy within 6 months	160 (8%)	166 (9%)
10-year Tyrer-Cuzick risk (%)	7·6% (5·8–9·9)	7·8 (5·1–10·2)

Data are median (IQR) or n (%).

***Table 1:* Baseline characteristics**

***Entry criteria and distribution by treatment allocation*:**

For women aged 45-70	**Anastrozole (N=1920)**	**Placebo (N=1944)**
First degree relative who developed breast cancer at age 50 or less.	677 (35.3%)	655 (33.7%)
First degree relative who developed bilateral cancer.	164 (8.5%)	141 (7.3%)
Two or more first or second degree relatives who developed breast or ovarian cancer.	952 (49.6%)	933 (48.0%)
Nulliparous or age 30 or above at first birth, and first degree relative who developed breast cancer.	211 (11.0%)	207 (10.6%)
Benign biopsy with proliferative disease and first degree relative who developed breast cancer.	21 (1.1%)	33 (1.7%)
Mammographic opacity covering at least 50% of the breast	7 (0.4%)	10 (0.5%)
First degree relative with breast cancer at any age.	488 (25.4%)	499 (25.7%)
Age at menopause 55 years or more.	45 (2.3%)	38 (2.0%)
Nulliparous or age 30 or above at first birth.	86 (4.5%)	83 (4.3%)
For women aged 40-44		
Two or more first or second degree relatives who developed breast cancer or ovarian cancer at age 50 or less.	8 (4.2%)	8 (0.4%)
First degree relative with bilateral breast cancer who developed first breast cancer at age 50 or less.	2 (0.1%)	0
Nulliparous or age 30 or above at first birth, and first degree relative who developed breast cancer at age 40 or less.	0	2 (0.1%)
Benign biopsy with proliferative disease and first degree relative who developed breast cancer at age 40 or less.	0	0
For women in all age groups		
Lobular carcinoma in situ (LCIS)	50 (2.6%)	55 (2.8%)
Atypical ductal or lobular hyperplasia in a benign lesion.	104 (5.4%)	135 (6.9%)
DCIS (ER-positive) diagnosed within last 6 months with completed adequate local treatment.	160 (8.3%)	166 (8.5%)
Women with a clearly apparent family history indicating appropriate increased risk	34 (1.8%)	38 (2.0%

ER = Oestrogen Receptor, LCIS = Lobular Carcinoma In Situ, DCIS = Ductal Carcinoma In Situ

Baseline characteristics and family history were evenly matched between the anastrozole group and the placebo group.

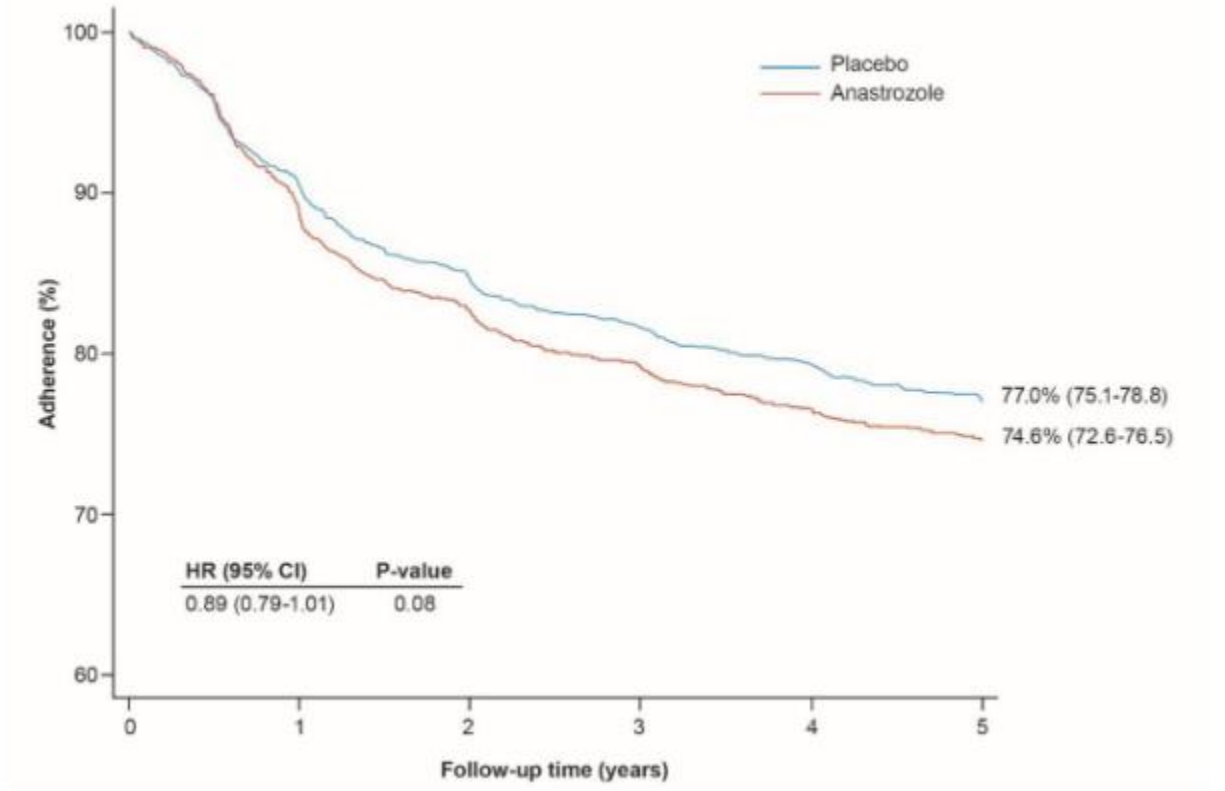
Median age at study entry was 59·4 years (IQR 55·0–63·4), 1893 women (47·0%) had used hormone replacement therapy before entering the trial, and 2631 (68·1%) had a BMI of more than 25kg/m².

Results

<u>Adherence to 5 years of treatment</u>

The treatment protocol for this study required 5 years of treatment and so the adherence of patients to these requirements was an important consideration. An analysis of adherence within IBIS-II showed that there was no significant difference between anastrozole and placebo (p=0.081). Over the 5-year treatment period, adherence in the anastrozole group was 74.6% compared to 77.0% in the placebo group (HR 0.89, 95% CI 0.79–1.01, p=0.081).

***Graph of 5-year adherence to allocated treatment*:**



5-year analysis (data cut-off 15 May 2013)

Median follow-up for the 5-year analysis was 60 months (IQR 36–85) [ie. 5.0 years (IQR 3.0 – 7.1)].

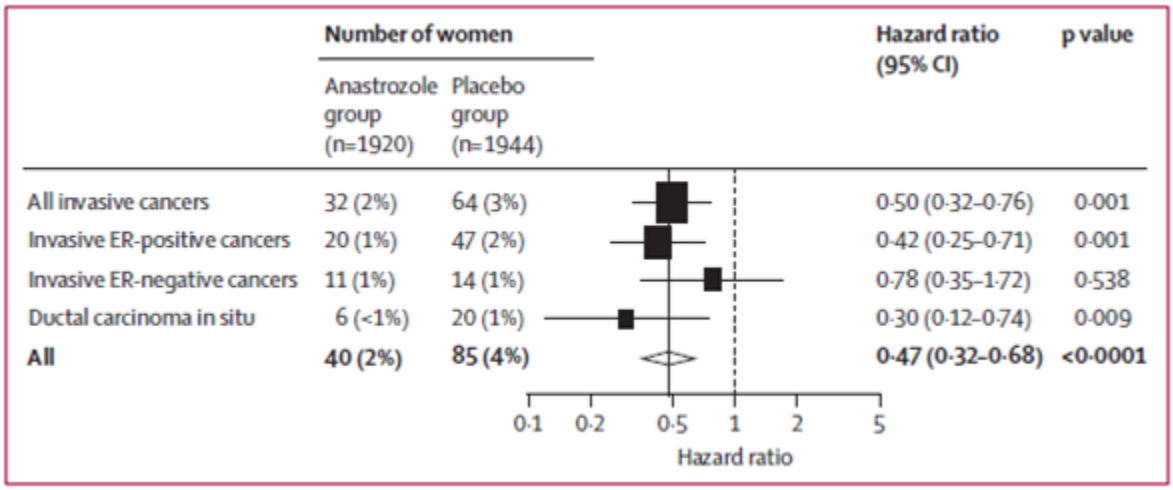
19 399 women-years of follow-up had been accrued (9727 in the anastrozole group *vs* 9672 in the placebo group).

At the time of data lock, 979 women (51%) in the anastrozole group and 975 (50%) in the placebo group had completed 5 years of treatment.

At the cut-off date, 357 women (19%) in the anastrozole group and 450 (23%) in the placebo group were continuing with treatment.

An analysis of the primary endpoint demonstrated that there were significantly fewer breast cancer cases (including ductal carcinoma in situ) in the anastrozole group (n=40, 2%) in comparison to the placebo group (n=85, 4%; HR 0.47, 95% CI 0.32–0.68, p<0.0001) at this time point.

***Analyses by type of breast cancer*:**
Numbers in subgroups do not match totals because of missing data. ER=oestrogen receptor.



Long-term follow-up analysis (12 years)
As there is a potential for a long-term term reduction in breast cancer incidence (and for the full benefits of treatment to be realised over a long period), additional long-term follow-up was undertaken in the post-treatment period. Women were followed on a yearly basis to collect data on breast cancer incidence, death, other cancers, and major adverse events (cardiovascular events and fractures).

Primary and secondary endpoints of this long-term analysis remained consistent with the 5-year follow-up.

All analyses were done using the intention-to-treat group and included all randomised patients. Analyses of efficacy endpoints were conducted using Cox proportional hazard models. Survival curves were estimated using the Kaplan-Meier method.

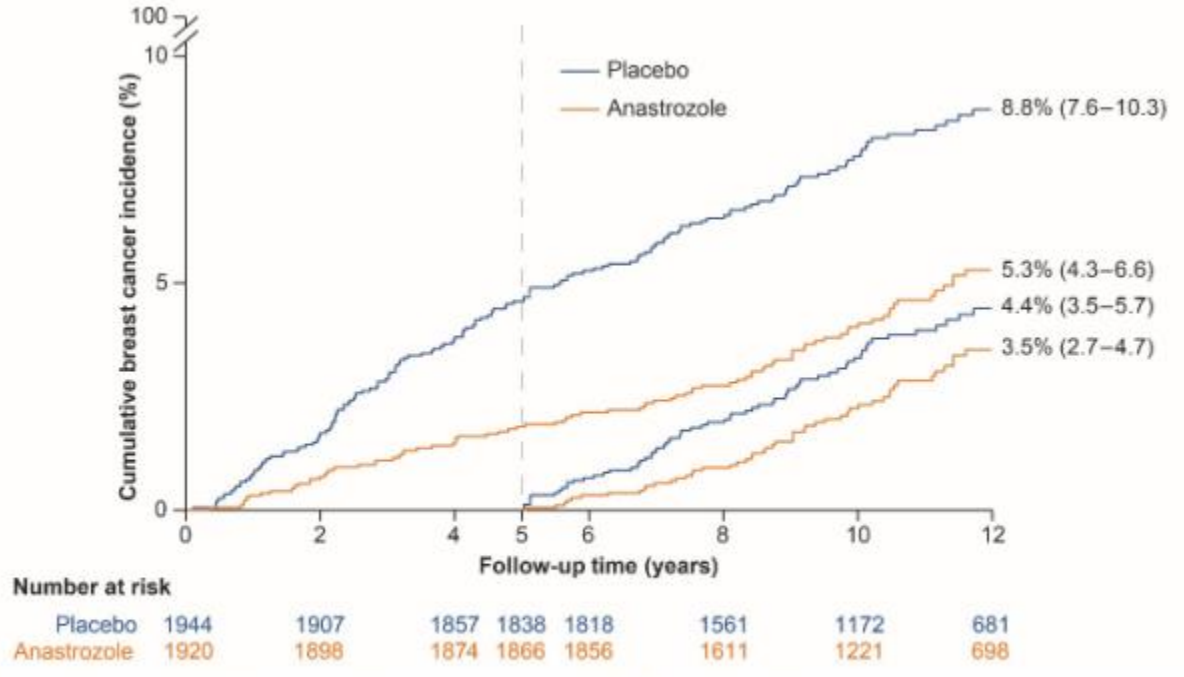
At the end of the 5-year treatment period, 3704 patients (95·9%) were still at risk of developing breast cancer (1866 in anastrozole group, 1838 in placebo group).

Mean follow-up for this long-term analysis was 131 months (IQR 106–156), which consisted of a total of 41,295 women-years of follow-up (20,803 women-years for anastrozole and 20,491 women-years for placebo), of this 22,367 women-years came after the 5-year treatment period.

At this time-point, it was found that there was a significant reduction in breast cancer cases in the anastrozole group (n=85, 4.4%) compared to placebo (n=165, 8.5%, p<0.0001). This corresponds to a 49% reduction for all breast cancer cases with anastrozole (HR 0.51, 95% CI 0.39–0.66, p<0.0001).

A Kaplan-Meier survival curve was constructed which allowed the calculation of an estimated risk of breast cancer during the 12-year follow-up period. These figures were calculated to be 5.3% (IQR 4.3–6.6) in the anastrozole group *versus* 8.8% (IQR 7.6–10.3) in placebo group. Based on these results, anastrozole had a number needed to treat of 29 in order to prevent one breast cancer case (over 12 years).

***Kaplan-Meier cumulative incidence of breast cancer*:**



The graph plots risk from start of treatment (0 years) and risk after the end of active treatment (5 years) to show comparison of risk reduction over 0–5 years period and post–5 years period.

***Breast cancer rate outcomes and subgroup analyses*:**

	Number of events		HR (95% CI)	p-value	$p_{heterogeneity}$
	Anastrozole	Placebo			
All breast cancer					
Overall	85	165	0.51 (0.39–0.66)	<0.0001	–
0-5 years	35	89	0.39 (0.27–0.58)	<0.0001	0.087*
>5 years	50	76	0.64 (0.45–0.91)	0.014	–
Invasive breast cancer					
All invasive	71	132	0.53 (0.40–0.71)	<0.0001	–
Invasive ER+	48	103	0.46 (0.33–0.65)	<0.0001	–
0-5 years	20	51	0.39 (0.23–0.66)	<0.0001	0.43*

	Number of events		HR (95% CI)	p-value	$p_{heterogeneity}$
	Anastrozole	Placebo			
>5 years	28	52	0.52 (0.33–0.83)	0.0062	–
Invasive ER-	17	22	0.77 (0.41–1.44)	0.4225	–
Ductal carcinoma in situ					
All DCIS	13	31	0.41 (0.22–0.79)	0.0081	–
0-5 years	5	17	0.29 (0.11–0.80)	0.016	0.43*
>5 years	8	14	0.56 (0.23–1.32)	0.18	–
ER+ DCIS	4	18	0.22 (0.07–0.65)	0.0077	–
Subgroup analyses					
Nodal status					
Negative	35	88	0.39 (0.27-0.58)	<0.0001	–
Positive	26	32	0.80 (0.48-1.34)	0.4014	0.083†
Tumour grade					
Low	14	17	0.81 (0.40-1.65)	0.5716	–
Intermediate	33	72	0.45 (0.30-0.68)	0.0001	–
High	21	39	0.53 (0.31-0.91)	0.0207	0.18†
Tumour size					
≤10mm	17	41	0.41 (0.23-0.72)	0.0022	–
10-20mm	26	48	0.53 (0.33-0.86)	0.0094	–
>20mm	28	43	0.64 (0.40-1.03)	0.0640	0.31†
HER2 status					
Negative	58	101	0.57 (0.41-0.78)	0.0006	–
Positive	9	17	0.52 (0.23-1.17)	0.1150	0.86†
Age					
≤55 years	17	32	0.51 (0.28-0.91)	0.0249	–
55-60 years	13	44	0.32 (0.17-0.59)	0.0004	–
>60 years	41	56	0.70 (0.47-1.05)	0.0816	0.5†
Body mass index					
≤25 kg/m^2	17	28	0.59 (0.32-1.07)	0.0863	–
25-30 kg/m^2	27	45	0.61 (0.38-0.98)	0.0405	–
>30 kg/m^2	27	57	0.46 (0.29-0.73)	0.0010	0.66†
HRT					
Never	36	74	0.48 (0.32-0.71)	0.0003	–
Prior	35	58	0.60 (0.39-0.91)	0.0180	0.46†
Benign breast disease					
LCIS or AH	8	23	0.34 (0.15-0.77)	0.0097	–
No LCIS or AH	63	109	0.57 (0.42-0.78)	0.0004	0.21†

*0–5 years *vs* >5 years. †Comparison within subgroups. AH: atypical hyperplasia; CI: confidence intervals; DCIS: ductal carcinoma in situ; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; HRT: hormone replacement therapy; LCIS: lobular carcinoma in situ

These results show that the reduction in breast cancer incidence with anastrozole over placebo was greatest during the 5 years of treatment (HR 0.39, 95% CI 0.27–0.58, p<0.0001), with a smaller (but still significant) reduction seen over the subsequent follow-up period (HR 0.64, 0.45–0.91, p=0.014). An analysis of heterogeneity showed there was no significant difference in treatment effects between the two periods (p=0.087).
The analysis conducted by tumour type showed significant reductions with anastrozole over placebo in most tumour types analysed. The results for invasive cancers and ER+ invasive cancers matched the overall results quite closely. The most noticeable difference was in the

ER- invasive cancers, where there was no significant difference between anastrozole and placebo (although there were lower numbers of ER- tumours and the measured rates showed a numerical advantage for anastrozole). For ductal carcinoma in situ, much fewer cases were seen, limiting the conclusions that can be drawn; but a significant reduction was seen in all ductal carcinoma in situ, ductal carcinoma in situ over the first 5 years of treatment, and ER+ ductal carcinoma in situ. This suggests that the efficacy seen in other tumour types is maintained here despite the lack of significance in all results within this tumour type.

Adverse events

The major analysis of all adverse events (AEs) was undertaken at the 5-year timepoint.

A summary of adverse events is given in the table below, which includes all predefined AEs, AEs affecting at least 5% of participants, or those that differed significantly (p<0.02) between groups.

***Adverse events recorded in IBIS-II study during period of medication usage*:**

	Anastrozole group (n=1920)	Placebo group (n=1944)	Risk ratio (95% CI)
Any	1709 (89%)	1723 (89%)	1·00 (0·98–1·03)
Fractures	164 (9%)	149 (8%)	1·11 (0·90–1·38)
Arm	66 (3%)	61 (3%)	1·10 (0·78–1·54)
Leg	65 (3%)	57 (3%)	1·15 (0·81–1·64)
Rib, spine, or collarbone	23 (1%)	18 (1%)	1·29 (0·70–2·39)
Pelvic or hip	9 (<1%)	10 (1%)	0·91 (0·37–2·24)
Skull	1 (<1%)	1 (<1%)	1·01 (0·06–16·18)
Musculoskeletal	1226 (64%)	1124 (58%)	1·10 (1·05–1·16)
Arthralgia*	972 (51%)	894 (46%)	1·10 (1·03–1·18)
Mild	385 (20%)	386 (20%)	1·01 (0·89–1·15)
Moderate	422 (22%)	363 (19%)	1·18 (1·04–1·33)
Severe	151 (8%)	123 (6%)	1·24 (0·99–1·56)
Joint stiffness	143 (7%)	96 (5%)	1·51 (1·17–1·94)
Pain in hand or foot	178 (9%)	147 (8%)	1·23 (0·99–1·51)
Carpal tunnel syndrome or nerve compression	67 (3%)	43 (2%)	1·58 (1·08–2·30)
Vasomotor*†	1090 (57%)	961 (49%)	1·15 (1·08–1·22)
Mild	550 (29%)	504 (26%)	1·10 (1·00–1·22)
Moderate	390 (20%)	330 (17%)	1·20 (1·05–1·37)
Severe	150 (8%)	127 (7%)	1·20 (0·95–1·50)
Gynaecological	460 (24%)	423 (22%)	1·10 (0·98–1·24)
Vaginal dryness	357 (19%)	304 (16%)	1·19 (1·03–1·37)
Haemorrhage or bleeding	65 (3%)	81 (4%)	0·82 (0·60–1·13)
Vaginal or uterine prolapse	13 (1%)	31 (2%)	0·42 (0·22–0·81)
Vulvovaginal pruritus	40 (2%)	60 (3%)	0·68 (0·45–1·00)
Vascular	152 (8%)	127 (7%)	1·27 (0·97–1·52)
Hypertension	89 (5%)	55 (3%)	1·64 (1·18–2·28)
Myocardial infarction or cardiac failure	8 (<1%)	9 (<1%)	0·90 (0·35–2·32)
Thrombosis or embolism	19 (1%)	17 (1%)	1·13 (0·59–2·17)
Phlebitis	9 (<1%)	8 (<1%)	1·14 (0·44–2·95)
Cerebrovascular accident	3 (<1%)	6 (<1%)	0·51 (0·13–2·02)
Eye	348 (18%)	335 (17%)	1·05 (0·92–1·21)
Dry eyes	83 (4%)	58 (2%)	1·45 (1·04–2·01)
Conjunctivitis	12 (1%)	5 (<1%)	2·43 (0·86–6·88)
Glaucoma	12 (1%)	24 (1%)	0·51 (0·25–1·00)
Cataract	90 (5%)	95 (5%)	0·96 (0·72–1·27)
Infections	230 (12%)	217 (11%)	1·07 (0·90–1·28)
Influenza	25 (1%)	12 (1%)	2·11 (1·06–4·19)
Otitis media	18 (1%)	6 (<1%)	3·04 (1·21–7·64)

Data are n (%), unless otherwise stated. Details of any reported adverse event were recorded at every follow-up visit. Adverse events shown here are those that were predefined, common (affecting at least 5% of participants), or differed significantly (p<0·02) between groups. *Assessments of severity broadly based on Common Terminology Criteria for Adverse Events, but some discretion used by clinicians. †Hot flushes or night sweats.

Table 4: **Adverse events of any severity reported at any time**

In brief, fractures (total and within group types) did not differ significantly between treatment groups. It was noted that concomitant bisphosphonate use was similar between treatment groups:17% (330/1920) in patients receiving anastrozole and 15% (297/1944) in those receiving placebo. Within the anastrozole group, there were significantly higher reports than in the placebo group for musculoskeletal AEs (p=0.0001), moderate arthralgia (p=0.01), carpal tunnel syndrome (p<0.05), joint stiffness (p<0.05), vasomotor symptoms (p<0.0001), dry eyes (p<0.05), and hypertension (p<0.05). However, despite these differences, no significant differences were seen for mild (p=0.9) or severe (p=0.06) arthralgia, thromboembolic events, cerebrovascular events, or myocardial infarction. Vaginal or uterine prolapse and vaginal pruritus were significantly (p<0.05) reduced in the anastrozole group compared to placebo. Hypercholesterolemia was not a commonly reported AE in this trial and no difference was observed between placebo and anastrozole.

Safety results from long-term follow-up
After the end of the 5-year treatment period, only major AEs (defined as other cancers, cardiovascular events, fractures, and deaths) were routinely collected. Comparison between groups for these outcomes was undertaken using ORs and Fisher exact tests.

Overall, there was no significant difference between anastrozole and placebo for any of these events. Of note was that there was no excess of fractures during the follow-up period (anastrozole 380 *vs* placebo 373, OR 1.04, 95% CI 0.88–1.22). There was a numerical increase in fractures for the anastrozole group, but a subgroup analysis looking at the 5-year treatment period *versus* the period after 5 years showed that any increase in fracture risk appeared to occur during the treatment period only (OR during 5-year treatment period 1.09, 0.87–1.35 and OR for post 5-year period 0.98, 0.79–1.23). Myocardial infarctions and deep vein thromboses appeared to be relatively evenly distributed between treatment groups. Pulmonary embolism, transient ischaemic attack and stroke all appeared to be slightly increased within the anastrozole group compared to placebo, but in all cases the differences were not significant.

***Major adverse events in long-term follow-up*:**

	Anastrozole (n=1920) Number of women	Placebo (n=1944) Number of women	Odds ratio (95% CI)	p-value
Fractures	380	373	1.04 (0.89–1.22)	0.648
Cardiovascular events (all)*	93	80	1.19 (0.87–1.61)	0.278
Myocardial infarction	16	14	1.16 (0.56–2.38)	0.702
Deep vein thrombosis†	13	17	0.77 (0.37–1.60)	0.496
Pulmonary embolism	17	12	1.44 (0.69–3.02)	0.342
Transient ischaemic attack#	24	20	1.22 (0.67–2.21)	0.528
Stroke	23	17	1.37 (0.73–2.58)	0.328

Data presented as all years (>5 years). *In the absence of pulmonary embolism. †In the absence of stroke.

During this long-term follow-up, an analysis of all other cancers (*i.e.* cancers that were not breast cancer) was also carried out. This analysis found a reduction in these cancers within the anastrozole group compared to the placebo group (OR 0.72, 95% CI 0.57–0.91,

p=0.0042), mainly driven by a reduction in non-melanoma skin cancer (OR 0.59, 0.39–0.87, p=0.0058).

***Cancers other than breast*:**

	Anastrozole (n=1920)	Placebo (n=1944)	Odds ratio (95% CI)
Total	147 (7.1%)	200 (9.8%)	0.72 (0.57–0.91)
Skin	52 (2.7%)	85 (4.4%)	0.61 (0.42–0.88)
Non-melanoma	43 (2.2%)	73 (3.8%)	0.59 (0.39–0.87)
Melanoma	9 (0.5%)	12 (0.6%)	0.76 (0.28–1.97)
Gynaecological	14 (0.7%)	20 (1.0%)	0.71 (0.33–1.47)
Endometrial	5 (0.3%)	7 (0.4%)	0.72 (0.18–2.65)
Ovarian	7 (0.4%)	10 (0.5%)	0.71 (0.23–2.06)
Respiratory	13 (0.7%)	13 (0.7%)	1.01 (0.43–2.38)
Lung	11 (0.6%)	12 (0.6%)	0.93 (0.37–2.30)
Gastrointestinal	24 (1.3%)	33 (1.7%)	0.81 (0.45–1.43)
Colorectal	11 (0.6%)	16 (0.8%)	0.69 (0.29–1.60)

Data presented as n (%). CI: confidence intervals.

139 patients (3·6%) died during the study (69 anastrozole *vs* 70 placebo), with no difference between the two treatment groups (HR 0·96, 95% CI 0·69–1·34, p=0·82). Only five breast cancer deaths (three in anastrozole group *vs* two in placebo group) were recorded. With this small number, it was not possible to assess any impact on breast cancer mortality within this study. Deaths from cancers other than breast did not differ between treatment groups (p=0·39).

***Causes of death*:**

	Anastrozole, N=1920, n (%)	Placebo, N=1944, n (%)	Hazard ratio (95% CI)
All	69 (3·6%)	70 (3·6%)	0·96 (0·69–1·34)
Breast cancer	2 (0·1%)	3 (0·2%)	0·64 (0·11–3·88)
Other cancer	27 (1·4%)	34 (1·8%)	0·77 (0·47–1·28)
Cardiovascular	13 (0·7%)	9 (0·5%)	1·41 (0·60–3·31)
Other or unknown	27 (1·4%)	24 (1·2%)	1·10 (0·63–1·91)

Table 4: Specific causes of death

Bone health

An additional analysis of bone health within the IBIS-II study was conducted (Sestak *et al*. 2014) Within this analysis, patients were enrolled from the main IBIS-II study into three stratified groups depending on baseline T score:

- Stratum I, women with healthy T score (at least –1·0);
- Stratum II, women who were osteopenic (T score at least –2·5 but less than –1·0);
- Stratum III, osteoporotic women with a T score of less than –2·5 but greater than –4·0 or those with one to two low trauma fragility fractures (as assessed by spinal radiographs from up to 2 years before randomisation).

Exclusion criteria included: previous bilateral hip fractures; any type of metabolic bone disease; women who had regularly taken medication that can affect bone metabolism within

the 12 months before randomisation; and women with a T score of less than –4·0 or more than two low trauma fractures (excluded and referred for further management).
Treatment
Stratum I was followed with no additional treatment.
Stratum II was randomised to either 35mg/week risedronate or a matched placebo for 5 years.
Stratum III received 35mg/week risedronate for 5 years.

Dose reductions or treatment holidays were allowed if patients developed severe adverse events potentially related to risedronate. All women were advised to take vitamin D and calcium supplements, but no doses were specified or required.

Women were removed from the bone study under the following conditions: withdrew from IBIS-II main study, developed breast cancer, death, or rapid bone loss occurred.

Investigations
Bone density was assessed in all IBIS-II participants at baseline and the bone study included additional DEXA scans of the lumbar spine and total hip at 12, 36, and 60 months. Bone loss above certain thresholds led to additional DEXA scans for safety. All DEXA scans were centrally reviewed by two expert clinical scientists to ensure quality and consistency.

A 10mL urine sample from the second void was used for biomarker analysis (at baseline and 12 months). N-telopeptide of type I collagen (NTx) levels were measured using the Ortho Clinical Diagnostics automated immunoassay (High Wycombe, UK) and expressed as a ratio to creatinine.

Endpoints
The primary objective of the bone substudy was to compare the effect of risedronate *versus* placebo on bone density in women taking anastrozole (Stratum II).

Secondary endpoints included: effects on bone mineral density in all women not allocated risedronate (including healthy women); effect of anastrozole *versus* placebo on bone density in osteoporotic women (Stratum III); and changes in biochemical markers (NTx to creatinine ratio) between baseline and 12 months in all patient groups.

Analysis
Power calculations were conducted which provided a target sample size of 500 women *per* group (healthy/osteopenic/osteoporotic). This was calculated to be able to detect a difference of 1.6% between risedronate and placebo with 90% power in Stratum II, and a difference of 1.4% between anastrozole and placebo with 90% power in Stratum I and Stratum III. Recruitment of osteoporotic women proved challenging and the target was not achieved. Recruitment was halted when 500 osteopenic women had been recruited to provide sufficient power for the primary study objective.

All analyses in this study were conducted on a *per protocol* basis, with women included if both a baseline and 36-month DEXA scan were available.

Main results were analysed as percentage mean bone mineral density changes with corresponding 95% CIs. Bone mineral density changes and differences between treatment groups were assessed using t tests for two independent samples with 95% CI. The NTx (N-telopeptide) to creatinine ratio was reported as estimated median percentage change with corresponding 95% CI. All p-values were two-sided and based on normal approximation.

Results of IBIS-II bone substudy

A total of 1410 women from IBIS-II were enrolled into the bone substudy.
Stratum I: n = 761
Stratum II: n = 500
Stratum III: n = 149

Baseline and 36-month DEXA scans were available for 903 (64%) women, who were included in the analysis.

Patients not included had withdrawn from IBIS-II study (199 Stratum I, 127 Stratum II, 32 Stratum III), withdrawn from the bone study (23 Stratum I, 49 Stratum II, 4 Stratum III), developed breast cancer (28 Stratum I, 12 Stratum II, 4 Stratum III), died (9 Stratum I, 4 Stratum II, 3 Stratum III [none of the deaths were assessed to be treatment related]), or had a bone density decrease of more than 6% at 12-month check-up and did not continue with the trial medication (8 Stratum I, 5 stratum II).
There were no significant differences in patient baseline characteristics detected between groups, except that women in Stratum III receiving placebo were, on average, older than those receiving anastrozole (p=0.043).

***Baseline characteristics for women in the bone substudy*:**

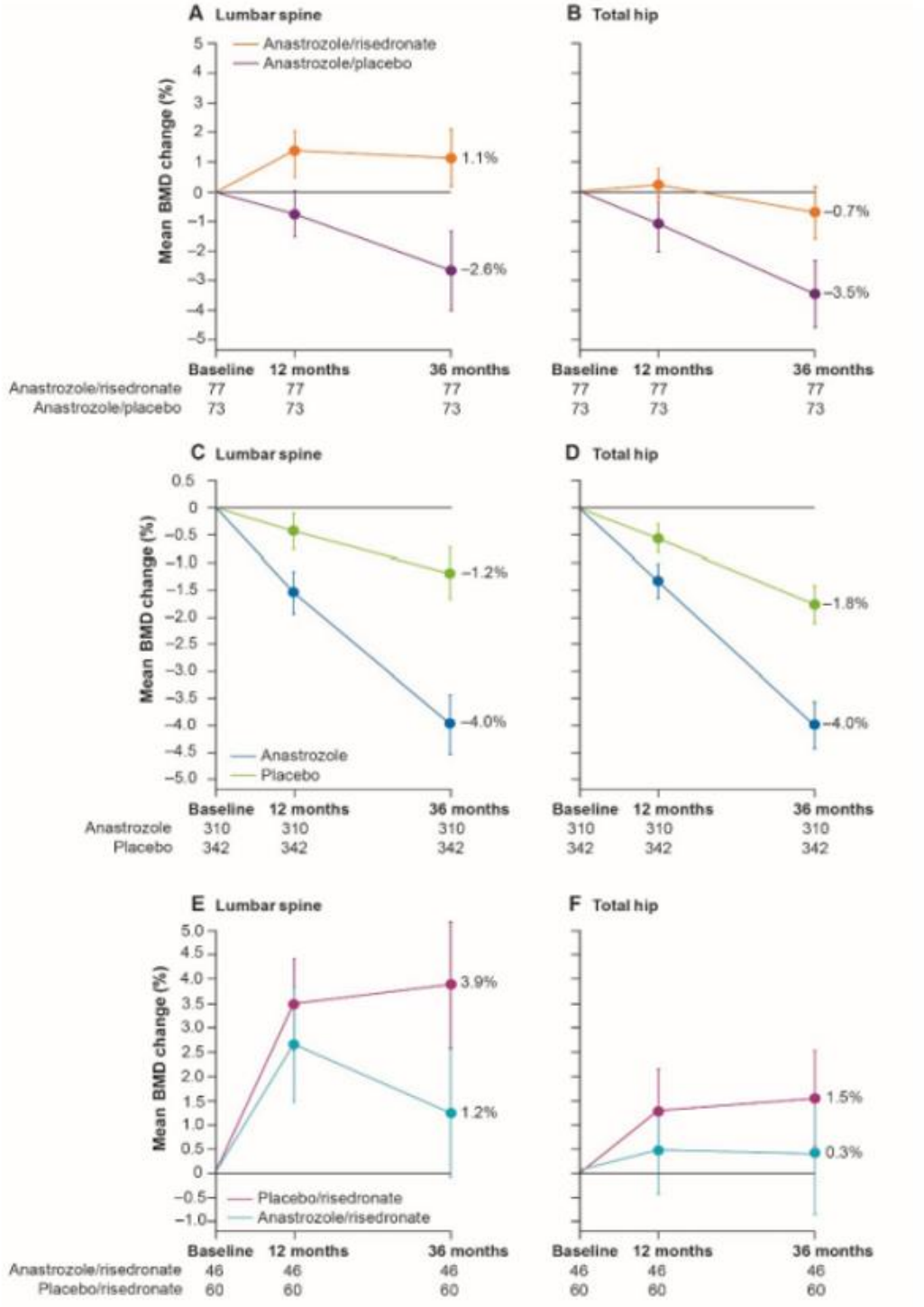
	Stratum I		Stratum II				Stratum III	
	P (n=257)	A (n=237)	P/P (n=85)	P/R (n=68)	A/P (n=73)	A/R (n=77)	P/R (n=60)	A/R (n=46)
Age (years)	58·7 (54·1–62·3)	58·4 (54·8–61·9)	59·4 (56·7–63·5)	60·8 (57·4–63·8)	60·2 (55·4–64·9)	60·0 (56·1–64·8)	61·9 (58·5–64·1)	59·3 (54·4–62·9)
Body-mass index (kg/m²)	28·7 (25·8–32·2)	28·6 (25·3–32·6)	27·1 (23·7–30·7)	26·4 (24·5–29·3)	26·3 (24·0–30·6)	26·4 (23·7–29·1)	26·3 (24·0–28·7)	25·4 (22·9–28·3)
Previous HRT use	129 (50%)	104 (44%)	35 (41%)	33 (45%)	31 (46%)	38 (49%)	23 (38%)	22 (48%)
Never smokers	156 (61%)	124 (52%)	54 (64%)	47 (64%)	39 (57%)	44 (57%)	37 (62%)	25 (54%)
Hysterectomy	80 (31%)	80 (34%)	21 (25%)	21 (29%)	21 (31%)	18 (23%)	18 (30%)	12 (26%)
Oophorectomy	47 (18%)	28 (12%)	8 (9%)	12 (16%)	11 (16%)	14 (18%)	3 (5%)	5 (11%)
Baseline T score	–0·22 (0·89)	–0·27 (0·82)	–1·40 (0·55)	–1·66 (0·53)	–1·44 (0·59)	–1·64 (0·62)	–2·64 (0·55)	–2·70 (0·56)

Data are median (IQR), n (%), or mean (SD). A: anastrozole; HRT: hormone replacement therapy; P: placebo; R: risedronate.

Within Stratum II, those women receiving anastrozole and risedronate showed a change in mean bone mineral density at the lumbar spine of +1.1% (95% CI 0.2 to 2.1) over 36 months *versus* a mean change of –2.6% (95% CI –4.0 to –1.3) in those receiving anastrozole alone (no risedronate) (p<0.0001, Figure A – see below). For the total hip, bone mineral density showed a change of –0.7% (95% CI –1.6 to 0.2) over 36 months in those receiving anastrozole and risedronate compared to –3.5% (–4.6 to –2.3, p=0.0001) in those receiving anastrozole alone (Figure B). This shows that at both sites, patients receiving anastrozole showed a linear bone mineral density loss that was significantly reduced by co-administration of risedronate. These conclusions were strengthened through analysis of patients in the other

strata. Women who received only anastrozole or placebo (no risedronate within Stratum I and Stratum II) showed a linear decrease in bone mineral density across all groups (Figure C & D).
In stratum III, increases in bone mineral density were seen across all groups (Figure E & F). The increase in bone mineral density at the lumbar spine was larger for those receiving placebo over those receiving anastrozole (+3.9% *vs* +1.2%, respectively, p=0.006). However, for the total hip, the difference between these groups was not significant (+1.5% *vs* +0.3%, p=0.12). At both sites, the increase in bone mineral density occurred mostly over the first 12 months and was maintained thereafter.

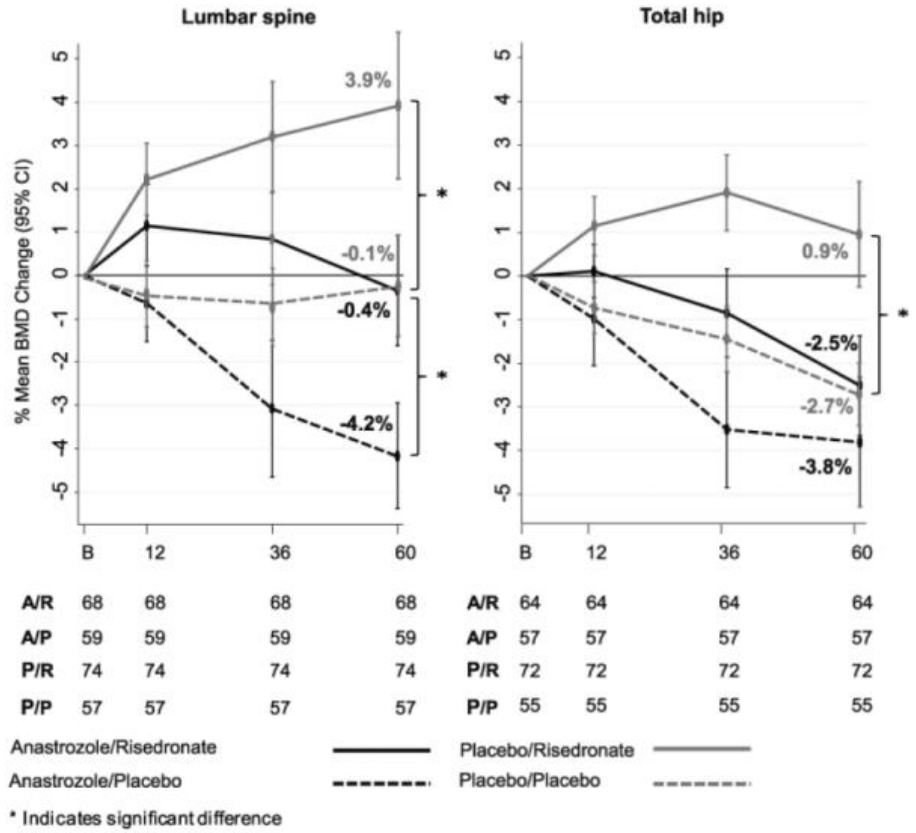
***Bone mineral density changes*:**



A & B – Stratum II patients receiving anastrozole split into those receiving risedronate or placebo. C & D – Stratum I or II patients not receiving risedronate split into those receiving anastrozole or placebo. E & F – Stratum III patients receiving risedronate split into those receiving anastrozole or placebo. Error bars show 95% confidence intervals.

The applicant also provided an additional analysis of the bone substudy including data for up to the full 5-year treatment period.

Mean percentage bone mineral density changes at lumbar spine and total hip at each follow-up visit for women in stratum II



Numbers below the figures show women at each follow-up visit with available DXA scan.

Number of women reporting fractures in bone substudy:

	Anastrozole	Placebo	Odds ratio (95% CI)	p-value
	Number of women	Number of women		
Fractures	50	47	0.98 (0.61–1.56)	0.927
Subgroup analyses				
No risedronate	30	29	1.02 (0.57–1.83)	0.853
Risedronate	20	18	0.91 (0.46–1.81)	0.849

The biochemical marker results provided supporting evidence and showed similar trends to that seen in the bone mineral density data.

***Results for N-telopeptide to creatinine ratios*:**

	Stratum I				
	Placebo (n=147)		Anastrozole (n=142)		p-value
Baseline	37.3 (34.7–39.8)		39.1 (35.8–42.3)		0.3
12 months	34.9 (31.5–38.3)		49.5 (45.3–53.6)		<0.0001
Median change*	–1.9% (–4.8 to 1.0)		8.9% (4.4 to 13.4)		<0.0001
p-value	0.5		<0.0001		
	Stratum II				
	P/P (n=70)	P/R (n=58)	A/P (n=69)	A/R (n=67)	p-value
Baseline	43.0 (36.4–49.7)	43.0 (35.3–50.6)	43.1 (34.8–51.3)	44.3 (38.7–50.0)	0.8
12 months	44.1 (39.4–48.9)	24.6 (17.6–31.6)	55.6 (49.7–61.6)	33.7 (28.3–39.1)	<0.0001
Median change*	–1.8% (–6.7 to 3.2)	–16.1% (–18.6 to –13.6)	11.7% (6.2 to 17.1)	–13.0% (–17.5 to –8.5)	<0.0001
p-value	0.3	<0.0001	0.0013	0.0002	
	Stratum III				
	Placebo (n=43)		Anastrozole (n=31)		p-value
Baseline	50.7 (43.8–57.6)		52.2 (45.1–59.4)		0.8
12 months	23.5 (16.5–30.5)		32.7 (23.1–42.3)		0.1
Median change*	–25.4% (–35.6 to –15.2)		–19.0% (–26.1 to –11.9)		0.3
p-value	<0.0001		0.0002		

Data presented as % (95% CI). *Median of individual differences between baseline and 12 months.
A: anastrozole; P: placebo; R: risedronate.

In Stratum I patients, a significant increase was seen for patients in the anastrozole group (p<0.0001) whereas no significant change was seen in the placebo group (p=0.5). Furthermore, comparison between treatment groups showed no significant difference at baseline (p=0.3), but there was a significant increase for anastrozole patients compared to placebo at 12 months (p<0.0001). In Stratum II, a significant increase was seen at 12 months for patients receiving anastrozole but not risedronate (p<0.0001); whereas those receiving risedronate showed a significant reduction whether they were receiving placebo (p<0.0001) or anastrozole (p=0.0002), and no significant change was seen in patients receiving placebo/placebo (p=0.3). Within Stratum III where all patients received risedronate, decreases in N-telopeptide to creatinine ratio were seen for both treatment groups (placebo, p<0.0001; anastrozole, p=0.0002). A between group comparison showed no significant difference between treatment groups in this stratum at baseline (p=0.8) and at 12 months (p=0.1).

Over the 3-year period of the bone substudy, 70.8% of patients experienced at least one AE (639/909), and these are summarised in Table 10. No significant differences in AE incidence were seen between treatment groups. No serious AEs (such as osteonecrosis of the jaw) were reported related to risedronate over the 3-year follow-up period. There were 85 patients who had a treatment interruption for risedronate. During the study period, two women in Stratum I (one anastrozole, one placebo) and 23 women in Stratum II (six placebo/placebo, two placebo/risedronate, ten anastrozole/placebo, and five anastrozole/risedronate) developed osteoporosis and exited the bone trial to start open-label bisphosphonate therapy.

Within this study, 128 fractures were reported by 109 patients, with 8% (57/711) of patients receiving anastrozole and 7% (52/699) of those receiving placebo reporting at least one

fracture. The number of fractures reported was too small in this substudy to undertake meaningful statistical analysis.

Discussion and benefit-risk conclusion

Efficacy

Evidence of the efficacy of anastrozole in the primary prevention setting comes from the IBIS-II study. This large, international, investigator-led randomised controlled trial showed that in a long-term analysis (11 years median follow-up) anastrozole led to a reduction of 49% in all breast cancer cases compared to placebo. This level efficacy led to a number needed to treat of 29 in order to prevent one breast cancer case.

Additional supportive evidence comes from the IBIS-I study that investigated tamoxifen for primary prevention of breast cancer (an indication for which this treatment is now licensed), which showed a reduction of around 30% in breast cancer cases. This a smaller reduction than seen with anastrozole, but further demonstrates the principle of primary prevention in a related treatment. Further evidence can be seen from the reduction in contralateral breast cancer cases seen in clinical trials for aromatase inhibitors.

Breast cancer risk assessment

The results from IBIS-II can be considered generalisable to UK clinical practice. The study included many UK centres and UK patients, and the dose and duration of treatment match that proposed in this variation. As the study began recruiting in 2003, there are questions as to how changes in clinical practice may affect the applicability of these results. The primary clinical factor needing consideration is the assessment of breast cancer risk. Breast cancer risk can be assessed using a number of validated tools and algorithms, however there is no universally agreed methodology employed. These tools use a variety of factors such as age, family history, genetics, reproductive history and breast density to calculate risk scores. A commonly used model is the Tyrer-Cuzick risk model (also known as the IBIS risk model as it was developed alongside the IBIS trials), and this was used in part during the IBIS-II study. The primary risk level required for enrolment in IBIS-II was based on an excess risk over the general population (four times higher for 40–44 years, two times higher risk for 45–60 years, and 1.5 times higher for 60–70 years). In addition, patients could be enrolled if their 10-year risk of breast cancer calculated by the Tyrer-Cuzick model was greater than 5%. These entry criteria for IBIS-II broadly correspond to a 10-year breast cancer risk of approximately 5% or more, using two of the most commonly used risk scoring tools, as illustrated in the table below.

***10-year breast cancer risk levels for general population and IBIS-II study*:**

Age	Population risk		Risk multiplier in IBIS-II entry criteria	Equivalent risk level of IBIS-II entry criteria	
	Tyrer-Cuzick v8	CanRisk		Tyrer-Cuzick v8	CanRisk
40	1.4%	1.7%	4x	5.6%	6.8%
50	2.3%	2.7%	2x	4.6%	5.4%
60	3.0%	3.5%	1.5x	4.3%	5.3%

Risk calculated based on age and no other risk factors using Tyrer-Cuzick v8 model,[18] and CanRisk model.[19]

NICE guidance in this area defines moderate risk for women aged 40–50 years as a 10-year risk of breast cancer of 3–8% and high risk as >8% (compared to a population rate of <3%). However, these criteria from NICE do not provide guidance on how breast cancer risk should

best be assessed and cover risk assessment in women of all ages (not just the postmenopausal target group relevant to anastrozole), meaning a more age-appropriate definition is preferrable for use in defining the patient population for anastrozole. The proposed licence variation uses a definition of risk that is age appropriate (given the average age of menopause is approximately 50 years), reflects the IBIS-II eligibility criteria, and represents a similar level of risk as the definitions used by NICE. Thus, the proposed indication for anastrozole includes those postmenopausal women with a 10-year risk of breast cancer of 5% or greater.

Over the past 20 years the assessment of breast cancer risk has evolved, including the role of breast density and certain gene variants as risk factors. Dense breasts with more fibroglandular tissue and less fat are now considered to be an independent risk factor for future breast cancer and is included as an input in the latest Tyrer-Cuzick model. The most frequent gene variants associated with hereditary breast cancer are the BRCA mutations (BRCA1 and BRCA2), albeit they remain relatively uncommon (<10% prevalence). As reflects practice at the time, neither of these risk factors was specifically assessed during recruitment to IBIS-II, although a retrospective analysis found a small number of women included with BRCA mutations. Overall, there is no reason to expect these risk factors to impact the generalisability of the study results.

Use of HRT
The use of HRT has continued to evolve over time. Prior to 2002, HRT was widely used within the UK; however, studies during the early 2000s led to safety concerns and a substantial drop in its usage. In the UK, HRT usage has remained lower than pre-2002 levels, but has elevated slightly over time. In a study on GP prescribing in 2018, it was found that there was a prescription rate of 187 HRT items *per* 1,000 women over 40 months. Therefore, current HRT usage is not fully reflected in the IBIS-II population. However, a subgroup analysis reported that efficacy was equivalent in patients who had never received HRT and those who had previously used HRT, and for both these groups efficacy was significantly improved over placebo. This gives confidence that previous HRT usage should not affect the efficacy of anastrozole at preventing primary breast cancer and the generalisability of the IBIS-II results.

Overall, changes in clinical practice since the start of IBIS-II can be considered not to be of major concern and unlikely to influence the efficacy of anastrozole seen through the trial. Whilst some evolution of risk assessment has occurred, in general, the risk profile of women within IBIS-II can be seen to be relevant to current practice and the proposed licensed indication.

Safety
The safety profile of anastrozole is well-known and data from its use in the adjuvant setting provides additional support at the same dosing schedule and length of treatment. The IBIS-II study revealed no additional safety concerns around the use of anastrozole.

Bone health was a key consideration within the IBIS-II study. The bone substudy showed that a negative effect on bone mineral density was detectable with anastrozole. However, this study also showed that bisphosphonate treatment was able to counteract the bone mineral density changes associated with anastrozole. In addition, through the IBIS-II study at 5-years and in the long-term follow-up there was no significant difference seen in overall fracture numbers between anastrozole and placebo groups. Further reassurance comes from the long-term study that reported any increased risk of fracture present appears to be associated with the period of anastrozole treatment, with risk reverting back to a level comparable to placebo

once treatment has ended. Within the IBIS-II study patients with a T score of <–4.0 were excluded, and so data on these patients is not available.

Another area of potential concern raised with aromatase inhibitors is related to hypercholesterolemia, hypertension and the impact on ischaemic heart disease. During the treatment period, the IBIS-II study found no increased rates of hypercholesterolemia, although hypertension was significantly more commonly reported in the anastrozole group compared to placebo. The impact of these changes was investigated in the long-term follow-up which showed no significant differences in pulmonary embolism, transient ischaemic attack and stroke between treatment groups (rates appeared to be numerically higher in the anastrozole group compared to placebo), and no detectable difference in rates of myocardial infarctions and deep vein thromboses. Whilst these data cannot totally eliminate the concern around these factors, they demonstrate that the risk remains low and not significantly increased from placebo.

Overall, the totality of evidence demonstrates that anastrozole is an effective and well-tolerated option to prevent primary breast cancer in postmenopausal women at increased risk.

Conclusion

This was a literature-based submission.

26 references were cited in the Clinical Overview, with emphasis on those relating to the IBIS-II study, an international, double-blind, randomised placebo-controlled trial of anastrozole for prevention of breast cancer in postmenopausal women at increased risk of developing the disease.

Other supportive evidence included reference to:

1. the use of tamoxifen as a primary preventive for women at high risk of breast cancer. Tamoxifen is approved for primary prevention of breast cancer in women at moderate or high risk in the UK
2. observed reduction in contralateral breast cancer cases when aromatase inhibitors (including anastrozole) had been used to treat primary breast cancer
3. known safety profile of anastrozole used in the adjuvant setting, which has the same dose and treatment length as that proposed for primary prevention (ie. anastrozole 1 mg once a day for 5 years)
4. NICE guideline recommending anastrozole for postmenopausal women at high risk of breast cancer and consideration of its use for those with moderate risk (currently off-label)

Advice was sought from the Commission of Human Medicines (CHM) on 26-27 January 2023 regarding the inclusion of the new indication and further clinical efficacy and safety information was requested from the applicant. Satisfactory data was subsequently submitted by the applicant.

The IBIS-II study showed that fewer women developed breast cancer in the anastrozole group (n=85, 4.4%) compared to the placebo group (n=165, 8.5%) over a median follow-up of 12 years, corresponding to a 49% reduction for all breast cancer cases with anastrozole (HR 0.51, 95% CI 0.39–0.66, p<0.0001). The anastrozole efficacy data compare favourably to those of tamoxifen in IBIS-I, which had HR of 0.71 (95% CI 0.60–0.83, p<0·0001) over a median follow-up period of 16 years (7.0% [251/3579 women] and 9.8 % [350/3575] in the

tamoxifen and placebo groups, respectively). The number needed to treat in order to prevent one breast cancer case is reported to be 29 for anastrozole and approximately 50 for tamoxifen.

Only a very small proportion of patients (<1%) were lost to outcome follow-up and this was consistent across the treatment groups.
Subgroup analyses of IBIS-II revealed that the most pronounced reduction was in the risk of invasive oestrogen-receptor-positive breast cancer and ductal carcinoma in-situ during the first 5 years of treatment, with little effect on the development of oestrogen-receptor negative cancer.

It is observed that women over the age of 60 did not derive as much benefit from anastrozole. The number of events in the anastrozole and placebo arms were 41 and 56, respectively; HR = 0.7, 95% CI 0.47 – 1.05). However, it is not considered necessary to introduce an age limit on the use of anastrozole in the primary prevention setting since women and their treating physicians will discuss benefits and risks on a case-by-case basis.

The safety profile of anastrozole is well-established.

The IBIS-II bone substudy publication confirmed anastrozole-induced loss of bone mineral density and showed that it could be improved with a bisphosphonate, risedronate, in the initial 3 years.

Apart from fractures, the total number of major adverse events (deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack and stroke) and deaths remain relatively small at the 12-year follow-up, therefore it is not possible to draw conclusion for these secondary endpoints.

Higher proportions of women had hypertension (includes terms essential hypertension, hypertension, accelerated hypertension, malignant hypertension and systolic hypertension), hypercholesterolaemia (includes terms hypercholesterolaemia, hyperlipidaemia and blood cholesterol increased) and cardiovascular events in the anastrozole arm than the placebo arm in IBIS-II. Even though p-values were not statistically significant, the odds ratios for these conditions were above 1, with 95% confidence intervals that were not excessively wide, thus suggesting a possible causal relationship. These findings have been included in the SmPC in order to alert the healthcare professionals to consider cardiovascular risks when starting anastrozole for primary prevention in healthy individuals as well as to consider anastrozole as a potential cause of new onset / deterioration of these conditions in those already on anastrozole.

Overall, the benefit-risk is positive. Anastrozole could be approvable for primary prevention of breast cancer, provided outstanding points are satisfactorily addressed.

The proposed changes are acceptable.

In accordance with legal requirements, the Summaries of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for the product granted Marketing Authorisation at a national level are available on the MHRA website.

Decision: Grant
Date: 06 November 2023.