

# FEASIBILITY of IBIS 3. An International Breast Intervention Study investigating prevention of late recurrence in ER+ breast cancer survivors following 5 years of adjuvant treatment

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<b>Registration date</b> 11/12/2014	<b>Overall study status</b> Stopped	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 18/06/2020	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

## Plain English summary of protocol

<https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-extended-treatment-following-5-years-hormone-therapy-breast-cancer-ibis-3-feasibility>

## Study website

[www.ibis-trials.org](http://www.ibis-trials.org)

## Contact information

### Type(s)

Public

### Contact name

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### Contact details

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Scientific

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## Additional identifiers

**EudraCT/CTIS number**

2014-004430-26

**IRAS number****ClinicalTrials.gov number**

Nil known

**Secondary identifying numbers**

Nil known

## Study information

**Scientific Title**

FEASIBILITY of IBIS 3. An International Breast Intervention Study investigating prevention of late recurrence in ER+ breast cancer survivors following 5 years of adjuvant treatment

**Acronym**

IBIS 3 (Feasibility)

**Study objectives**

IBIS 3 is designed to continue the work of IBIS-I and IBIS-II in determining whether a chemo-preventive strategy towards breast cancer is effective. Late recurrence of oestrogen receptor positive (ER+) breast cancer is a well-known problem, with high recurrence rates being seen for at least 20 years after diagnosis. In fact, over half of all recurrences in ER+ breast cancer occur more than 5 years after the primary tumour diagnosis. These include true recurrences and new primary tumours. Although reduced from about 2.5%/year with tamoxifen to 2%/year with 5 years of an aromatase inhibitor in the ATAC trial, the 10 year recurrence rate does not fall below 2%/year (Cuzick et al, 2010). The ATAC trial indicates that ER, PgR and HER2 do not provide

substantial prognostic information in the post 5-year treatment period. It shows that Ki-67 has a minimal effect whereas baseline nodal status and tumour size ( $\geq 2\text{cm}$ ) continue to have prognostic value (Sestak et al, 2013).

Late re-treatment of breast cancer is an important approach for dealing with the problem of late recurrence. Diminished endocrine control is well documented and other new or synergistic approaches are likely to be more effective. This approach will also inform on the preventive action of these agents both alone and in combination not only on elimination of metastases but also on new primary tumours. Because a substantial number of late recurrences are in fact new tumours, this approach will also inform on the preventive action of these agents both alone and in combination.

The main IBIS 3 trial will directly address the issue of late recurrence in breast cancer survivors. The main goal will be to reduce late recurrence with the combination of three different drug therapies. Specifically, it will evaluate the impact of metformin and/or an aromatase inhibitor (anastrozole or letrozole or exemestane) and/or zoledronic acid in a 2x2x2 factorial trial. Of particular interest will be any positive detection of any synergism between these agents.

The main trial will explore mechanisms of drug action and identify which patients are at greatest risk of late recurrence, including both local, regional and distant metastases of the primary tumour as well as new tumours (mostly contralateral), using a range of tests which may include circulating tumour DNA, IHC4, PAM50, and tumour methylation profiles.

This feasibility study will look at the viability of recruiting to the main trial; assess recruitment rates, inform on number of sites required for the main trial, treatment adherence and the use of recruiting through GP surgeries local to sites via the PCRN/LCRN. The study will also determine the feasibility of the use of email for data collection of PROs from patients and assess the acceptability of investigations, such as providing blood samples and questionnaires required for the main trial.

The decision rule for moving to the main trial will be recruitment of at least 80 patients within a year and that at least 20% of eligible patients approached agree to join the trial.

### **Ethics approval required**

Old ethics approval format

### **Ethics approval(s)**

Hampstead Ethics Committee, 08/06/2015, ref: 15/LO/0833

### **Study design**

Interventional multi-centre CTIMP RCT 2x2x2 factorial design

### **Primary study design**

Interventional

### **Secondary study design**

Randomised controlled trial

### **Study setting(s)**

Hospital

## **Study type(s)**

Treatment

## **Participant information sheet**

Not available in web format, please use the contact details below to request a patient information sheet

## **Health condition(s) or problem(s) studied**

Hormone receptor positive breast cancer recurrence

## **Interventions**

Metformin and zoledronic acid will be evaluated when combined with an aromatase inhibitor (anastrozole, letrozole or exemestane) in a 2x2x2 factorial design.

## **Intervention Type**

Drug

## **Phase**

Phase III

## **Drug/device/biological/vaccine name(s)**

Aromatase inhibitor (anastrozole, letrozole or exemestane), metformin, zoledronic acid

## **Primary outcome measure**

Primary objective is to determine acceptability and feasibility of recruitment, recruitment rate and number of sites required for main trial.

Primary endpoint is the recruitment of 100 patients within 12 months. Assessment method is recruitment numbers via randomisation figures and screening logs.

## **Secondary outcome measures**

Secondary objectives are:

1. To determine reasons for non-participation/drop-outs and address these for main trial (endpoint: recruitment and follow-up of 100 patients; assessment method: analysis of screening logs to understand reasons for non-participation)
2. To evaluate treatment adherence and reasons for stopping (endpoint: 6 monthly follow-up; assessment method: data collected on CRFs, PROs [FACT-ES, EQ5DL], Kaplan Meier curves)
3. To determine reasons for non-adherence and address for main trial (endpoint: 6 monthly follow-up; assessment method: data collected on CRFs, PROs [FACT-ES, EQ5DL])
4. To assess the use of referral through GP surgeries as PICs local to sites via the PCRN/LCRN (endpoint: the recruitment of 100 patients; assessment method: recruitment method captured by CRF and assessment of referral letters)
5. To investigate feasibility of the use of email for data collection of PROs from patients (enpoint: at baseline + asked again at 12 and 24 months to see if email use increases with time; assessment method: comparison of numbers of patients providing data by email or by post and quality and completeness of that data)
6. To assess acceptability of investigations for main trial (endpoint: at 12 months and ongoing until trial ends; assessment method: number of patients providing blood samples [data on CRF], PRO data [FACT-ES, EQ5DL])

## **Overall study start date**

01/01/2014

**Completion date**

26/03/2018

**Reason abandoned (if study stopped)**

Participant recruitment issue

## Eligibility

**Key inclusion criteria**

Current inclusion criteria as of 30/03/2017:

1. Informed Consent
2.  $\leq 75$  years
3. Post-menopausal women confirmed by previous AI use only
4. Previous ER+ breast cancer treated by endocrine therapy. ER+ is equivalent to an Allred/Quick score of 3 or above. Additional treatment with trastuzumab (if Her2+) and chemotherapy are allowed.
5. Surgery for breast cancer plus 5 years adjuvant endocrine therapy (at least 4 years with AI completed within the last 6 years; therefore 5-11 years from diagnosis)
6. Breast cancer must have been node positive AND/OR  $\geq 2$ cm in size (measurement based on invasive tumour)
7. A bilateral mammogram (unless unilateral mastectomy in which case unilateral mammogram) must have been taken within the last year and not show any evidence of breast cancer. Women who have had a bilateral mastectomy, where contralateral mastectomy was either prophylactic or was performed to treat breast cancers diagnosed at the same time, are eligible and a mammogram is not required in this case.
8. A baseline bone mineral density (BMD) scan within the last year; DXA must include hip (femoral neck or proximal femur) AND lumbar spine and can include forearm.
9. Low BMD (where T-score is  $-4.0 \leq T \leq -2.0$ ) women are eligible for metformin and aromatase inhibitor treatments. This must be managed in accordance with local clinical procedures for treatment of osteoporosis i.e., take bisphosphonate treatment and have regular DXA scans

Previous inclusion criteria:

1. Informed consent
2.  $\leq 75$  years old
3. Post-menopausal women (defined as at least 12 months since last period)
4. Previous ER+ (or PR+) breast cancer treated by endocrine therapy. ER+ is equivalent to an Allred/Quick score of 3 or above. Additional trastuzumab (if Her2+) and chemotherapy are allowed.
5. Surgery for breast cancer plus 4-6 years adjuvant endocrine therapy (at least 4 years with AI completed within the last 3 years; therefore maximum of 9 years from diagnosis)
6. Breast cancer must have been node positive (macrometastases) AND/OR  $\geq 2$ cm
7. A bilateral mammogram (unless unilateral mastectomy in which case unilateral mammogram) must have been taken within the last year and not show any evidence of breast cancer. Women who have had a bilateral mastectomy are eligible and a mammogram is not required in this case.
8. A baseline bone mineral density scan within the last year; DXA must include hip (femoral neck or proximal femur) AND lumbar spine and can include forearm.
9. Low BMD (where T-score is  $-4.0 \leq T \leq -2.0$ ) and no more than one known low trauma vertebral fracture AND/OR high FRAX score (<http://www.shef.ac.uk/FRAX/tool.aspx>) are eligible for

metformin and aromatase inhibitor treatments. This must be managed in accordance with local clinical procedures for treatment of osteoporosis i.e., take bisphosphonate treatment and have regular DXA scans.

**Participant type(s)**

Patient

**Age group**

Adult

**Sex**

Female

**Target number of participants**

300

**Total final enrolment**

89

**Key exclusion criteria**

Current exclusion criteria as of 30/03/2017:

1. Any recurrence or clinical suspicion of active breast cancer (including DCIS)
2. Any other previous cancer (apart from original breast cancer) (except non-melanoma skin cancer or in situ cancer of the cervix).
3. Current (or intended) use of oestrogen-based hormone replacement therapy (HRT)
4. Type I diabetes
5. Type II diabetes AND osteoporosis
6. T-scores of less than minus four, or two or more known low trauma vertebral fractures
7. Abnormal renal function as classified as eGFR < 45mls/min. – If possible the CKD-EP1 equation should be used to calculate eGFR but the Cockcroft-Gault formula is acceptable. See Appendix 3 for formulae and dose reduction schedule.
8. Any severe concomitant disease, e.g congestive cardiac failure, that would, at the discretion of the investigator, put patient at unusual risk or confounds the results of the study. Reference should be made to the appropriate Summary of Product Characteristics (SmPC) of each study drug
9. Current continual treatment with glucocorticoids for 4 weeks or more
10. Any medical condition that would significantly interfere with the ability to accept the study drugs.
11. Psychologically and physically unsuitable for two years of drug therapy.
12. Treatment with an unlicensed or experimental drug during 30 days before randomisation.

Excluded from metformin randomisation only

13. Type II diabetics (or those with baseline fasting glucose > 7.0 mmol/L) but must be on antidiabetic medication
14. Known hypersensitivity or intolerance to metformin
15. Currently taking meglitinides, sulfonylureas, thiazolidinediones (glitazones) or insulin
16. History of acidosis of any type
17. Habitual intake of 3 or more units of alcohol per day

Excluded from zoledronic randomisation only

18. Low BMD (where T-score is  $-4.0 \leq T \leq -2.0$ ). This must be managed in accordance with local

clinical procedures for treatment of osteoporosis i.e., take bisphosphonate treatment and have regular DXA scans. See Appendix 4 for definitions.

Excluded from AI randomisation only

19. Currently being treated by extended AI

20. Current use (or intention to use) raloxifene, tamoxifen or any other SERM

Previous exclusion criteria:

1. Any recurrence or clinical suspicion of active breast cancer (including DCIS)

2. Any other previous cancer (apart from original breast cancer) in the past 5 years (except non-melanoma skin cancer or in situ cancer of the cervix)

3. Current treatment (or intended use) of oestrogen-based hormone replacement therapy (HRT)

4. Type I diabetes

5. Diabetes (Types I and II) AND osteoporosis

6. T-scores of less than minus four, or two or more known low trauma vertebral fractures

7. Abnormal renal function as classified as eGFR < 40ml/min. If possible the CKD-EP1 equation should be used to calculate eGFR but the Cockcroft-Gault formula is acceptable

8. Any severe concomitant disease, e.g. congestive cardiac failure, that would, at the discretion of the investigator, put patient at unusual risk or confounds the results of the study. Reference should be made to the appropriate Summary of Product Characteristics (SmPC) of each study drug

9. Current continual treatment with glucocorticoids for 4 weeks or more

10. Any medical condition that would significantly interfere with the ability to accept the study drugs

11. Psychologically and physically unsuitable for two years of drug therapy

12. Treatment with an unlicensed or experimental drug during 30 days before randomisation

Excluded from metformin randomisation only:

1. Type II diabetics (or those with baseline fasting glucose > 7.0 mmol/L) but must be on antidiabetic medication

2. Known hypersensitivity or intolerance to metformin

3. Currently taking meglitinides, sulfonylureas, thiazolidinediones (glitazones) or insulin

4. History of acidosis of any type

5. Habitual intake of three or more units of alcohol per day

Excluded from zoledronic randomisation only:

1. Low BMD (where T-score is  $-4.0 \leq T \leq -2.0$ ) and no more than one known low trauma vertebral fracture AND/OR high FRAX score (<http://www.shef.ac.uk/FRAX/tool.aspx>)

Excluded from AI randomisation only:

1. Currently being treated by extended AI

2. Current use (or intention to use) raloxifene, tamoxifen or any other SERM

**Date of first enrolment**

26/09/2016

**Date of final enrolment**

26/09/2017

**Locations**

**Countries of recruitment**

England

Scotland

United Kingdom

Wales

**Study participating centre**

**Borders General Hospital**

Melrose

United Kingdom

TD6 9BS

**Study participating centre**

**Weston Park Hospital**

Sheffield

United Kingdom

S10 2SJ

**Study participating centre**

**Christie NHS Foundation Trust**

Manchester

United Kingdom

M20 4BX

**Study participating centre**

**Cardiff University Hospital NHS Trust**

Cardiff

United Kingdom

CF14 4XW

**Study participating centre**

**St Bartholomew's Hospital**

London

United Kingdom

EC1A 7BE



**Study participating centre**

**Ninewells Hospital**

Dundee

United Kingdom

DD1 9SY

**Study participating centre**

**Imperial College Healthcare NHS Trust**

Charing Cross Hospital

Fulham Palace Road

London

United Kingdom

W6 8RF

**Study participating centre**

**Doncaster Royal Infirmary**

Armthorpe Road

Doncaster

United Kingdom

DN2 5LT

**Study participating centre**

**Macclesfield District General Hospital**

Victoria Road

Macclesfield

United Kingdom

SK10 3BL

**Study participating centre**

**North Tyneside General Hospital**

Rake Lane

North Shields

United Kingdom

NE29 8NH

**Study participating centre**

**Pinderfields Hospital**

Aberford Road

Wakefield

United Kingdom

WF1 4DG

**Study participating centre****Western General Hospital**

Crewe Road  
Edinburgh  
United Kingdom  
EH4 2XU

**Study participating centre****Poole Hospital NHS Foundation Trust**

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## **Sponsor information**

**Organisation**

Queen Mary University of London

**Sponsor details**

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**Sponsor type**

University/education

**ROR**

<https://ror.org/026zzn846>

## **Funder(s)**

**Funder type**

Charity

**Funder Name**

Cancer Research UK

**Alternative Name(s)**

CR\_UK, Cancer Research UK - London, CRUK

**Funding Body Type**

Private sector organisation

**Funding Body Subtype**

Other non-profit organizations

**Location**

United Kingdom

**Funder Name**

Australia and New Zealand Breast Cancer Trials Group (ANZBCTG)

## Results and Publications

**Publication and dissemination plan**

Planned publication in a high-impact peer reviewed journal.

**Intention to publish date**

31/12/2020

**Individual participant data (IPD) sharing plan**

The datasets generated during and/or analysed during the current study are/will be available upon request from [ibis3@qmul.ac.uk](mailto:ibis3@qmul.ac.uk)

**IPD sharing plan summary**

Available on request

**Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Plain English results</a>				No	Yes
<a href="#">Basic results</a>			11/06/2020	No	No
<a href="#">Abstract results</a>	barriers to recruitment presented at 4th International Clinical Trials Methodology Conference (ICTMC) and the 38th Annual Meeting of the Society for Clinical Trials	01/05/2017	16/06/2020	No	No

