Clinical trial results:
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

Summary

EudraCT number	2014-004430-26
Trial protocol	GB
Global end of trial date	23 May 2018

Results information

Result version number	v1 (current)
This version publication date	05 January 2019
First version publication date	05 January 2019

Trial information

Trial identification

Sponsor protocol code	010207QM

Additional study identifiers

ISRCTN number	ISRCTN93764730
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	Joint Research Management Office QM Innovation Building, 5 Walden Street, London, United Kingdom, EC1M 6BQ
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 March 2018
Global end of trial reached?	Yes
Global end of trial date	23 May 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine acceptability and feasibility of recruitment, recruitment rate and number of sites required for a main trial. This larger trial will investigate the prevention of late recurrence with an aromatase inhibitor and/or metformin and/or zoledronic acid or standard care (no treatment) in high risk breast cancer survivors.

Protection of trial subjects:

Aromatase inhibitors (AIs) are associated with reduced bone-mineral density leading to increased risk of fracture. To address this concern a baseline bone density scan (DXA) will be performed on all women taking part in this randomisation to identify those who may have osteoporosis. In addition, osteopenic women randomised to an AI will be given a repeat DXA scan at final visit if last DXA was more than 12 months ago. Osteoporotic patients will be managed in accordance with local clinical procedures for treatment of such women i.e., take bisphosphonate treatment and have regular DXA scans.

For metformin. the initial side effect of bloating, nausea and diarrhoea will be mitigated by use of a run-in one month dose escalation. It is recommended that patients take loperamide (Imodium®) to help ease these side effects.

For zoledronic acid, osteonecrosis of the jaw (ONJ) is a rare complication. This complication is usually observed in cancer patients, probably due to the repeated dosage regimen and the prolonged exposure. The annual dosage regimen used in postmenopausal osteoporosis, on the other hand, is considered safe with regard to the risk of ONJ. Before zoledronic acid is initiated, patients should undergo an oral examination and appropriate preventive dentistry and be advised on maintaining good oral hygiene. Patients should avoid invasive dental procedures (extractions and implants) during therapy if possible. Any dental surgery must be completed before starting treatment on zoledronic acid. It is recommended that patients have a dental check-up within 6 months before randomisation in case any dental treatment is required, delaying zoledronic acid treatment.

Should any side effect become intolerable, the patient can try a treatment holiday, with the option of withdrawing from trial treatment always being an option.

Background therapy:

N/A

Evidence for comparator:

The evidence that aromatase inhibitors are effective as treatment for ER+ positive breast cancer in post-menopausal women is now overwhelming and has been summarised in an overview (Dowsett et al, 2010). The potential role of AIs in prevention has been reviewed by Cuzick et al (2011) and the IBIS-II trial confirmed the effectiveness of anastrozole in preventing breast cancer (Cuzick et al, 2014).
The appropriate duration of treatment of AIs is unclear. This trial will allow a randomised evaluation of the extension of the treatment interval by 2 years.

The evidence in favour of repurposing metformin as an active drug for breast cancer has recently been summarised (Thompson, 2014). In essence there is epidemiological, in vivo and human phase II and emerging phase III trial evidence. Two robust phase II trials in women with breast cancer (Hadad et al 2011; Niraula et al 2012), show that metformin reduces tumour proliferation and suppresses serum insulin levels. This is thought to work both through direct anti-tumour effects (via AMPK and mitochondrial mechanisms) and via systemic insulin based mechanisms.

Several randomised adjuvant studies have shown that bisphosphonates reduce the risk of recurrence in early breast cancer when used at the time of diagnosis (Powles et al, 2006; Ha et al 2007; Gnant et al, 2009; deBoer et al, 2011). Bisphosphonates have also been shown to abrogate the bone loss associated

with use of an AI, and to reduce recurrence and death rates in one trial when used in combination with either tamoxifen or an aromatase inhibitor after treatment with the LHRH (Luteinizing-hormone-releasing hormone) agonist goserelin in premenopausal women (ABCSG12: Gnant et al, 2009). Although negative results overall have also been reported in the AZURE trial (Coleman et al, 2011), there was a benefit in women who were more than 5 years past the menopause (most of the patients in this study will also have been post-menopausal for at least 4 years).

Actual start date of recruitment	27 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 89
Worldwide total number of subjects	89
EEA total number of subjects	89

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	40
From 65 to 84 years	49
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited over a 12 month period from 27th September 2016-26th September 2017 from 13 UK centres. Patients were recruited via breast cancer clinics at local sites and also via GPs acting as Patient Identification Centres (PICs).

Pre-assignment

Screening details:

434 patients were approached to join the study. Main reasons for non-participation included no response, not interested in clinical research, concerns of drug side effects, ineligible and no desire to undergo screening tests. 100 of those patients wanted to join but 11 of these failed screening tests (eGFR and insulin in blood samples & DXA scan)

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Aromatase Inhibitor

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 1mg daily dose of the AI will be taken orally, and should be swallowed whole with water. The tablet should be taken at the same time each day and it does not matter if it is taken before, with or after food. In the case a patient misses a dose or vomits she should continue to take one dose the next day. She should not double the dose.

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 25mg daily dose of the AI will be taken orally, and should be swallowed whole with water. The tablet should be taken at the same time each day and it does not matter if it is taken before, with or after food. In the case a patient misses a dose or vomits she should continue to take one dose the next day. She should not double the dose.

Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 2.5mg daily dose of the AI will be taken orally, and should be swallowed whole with water. The tablet should be taken at the same time each day and it does not matter if it is taken before, with or after food. In the case a patient misses a dose or vomits she should continue to take one dose the next day. She should not double the dose.

Arm title	Metformin
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 500mg daily from day to day 14; 1 x 850mg daily from day 15 to day 28; 1 x 850mg twice dailiy from day 29 to end of trial. The daily dose of metformin will be increased slowly up to one tablet taken twice daily, and will be taken orally. Serum creatinine should be measured at year 1 (if on zoledronic acid too this will be measured every 6 months) and treatment should be withheld if renal function has deteriorated (calculated eGFR < 45mls/min or > 20% reduction in eGFR from baseline).

The tablets should be taken at the same time each day with or just after food to lower the chance of stomach upset, and should be swallowed whole with water. In the case a patient misses a dose she should take one dose

Arm title	Zoledronic acid
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for dispersion for infusion, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

4mg/100ml solution for infusion OR 4mg/5ml concentrate for infusion

Arm title	No treatment

Arm description:

Randomised to no treatment - standard care at time when trial began

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	AI + Met
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 1mg daily dose of the AI will be taken orally, and should be swallowed whole with water. The tablet should be taken at the same time each day and it does not matter if it is taken before, with or after food. In the case a patient misses a dose or vomits she should continue to take one dose the next day. She should not double the dose.

Arm title	AI + ZA
Arm description: -	
Arm type	Experimental

Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 1mg daily dose of the AI will be taken orally, and should be swallowed whole with water. The tablet should be taken at the same time each day and it does not matter if it is taken before, with or after food. In the case a patient misses a dose or vomits she should continue to take one dose the next day. She should not double the dose.

Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A 2.5mg tablet taken orally once a day

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A 25mg tablet taken orally once a day

Arm title	Met + ZA

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 1mg daily dose of the AI will be taken orally, and should be swallowed whole with water. The tablet should be taken at the same time each day and it does not matter if it is taken before, with or after food. In the case a patient misses a dose or vomits she should continue to take one dose the next day. She should not double the dose.

Arm title	AI + Met + ZA

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 1mg daily dose of the AI will be taken orally, and should be swallowed whole with water. The tablet should be taken at the same time each day and it does not matter if it is taken before, with or after food. In the case a patient misses a dose or vomits she should continue to take one dose the next day. She should not double the dose.

Number of subjects in period 1	Aromatase Inhibitor	Metformin	Zoledronic acid
Started	6	19	16
Completed	6	14	11
Not completed	0	5	5
Patient choice due to other medical issues	-	-	-
Adverse event, non-fatal	-	1	1
Patient aware of premature end of study	-	1	-
Declined dental review	-	-	1
Patient had appointment changed and was unhappy	-	-	1
Protocol deviation	-	3	2

Number of subjects in period 1	No treatment	AI + Met	AI + ZA
Started	20	6	4
Completed	20	6	3
Not completed	0	0	1
Patient choice due to other medical issues	-	-	1
Adverse event, non-fatal	-	-	-
Patient aware of premature end of study	-	-	-
Declined dental review	-	-	-
Patient had appointment changed and was unhappy	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	Met + ZA	AI + Met + ZA
Started	15	3
Completed	13	3
Not completed	2	0
Patient choice due to other medical issues	-	-
Adverse event, non-fatal	-	-
Patient aware of premature end of study	-	-
Declined dental review	-	-
Patient had appointment changed and was unhappy	-	-
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)
Reporting group description:	
All randomised patients.	

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	89	89	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	40	40	
From 65-84 years	49	49	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	89	89	
Male	0	0	

Subject analysis sets	
Subject analysis set title	Final IBIS-3
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Final analysis of all 89 randomised patients into the IBIS-3 feasibility study.	

Reporting group values	Final IBIS-3		
Number of subjects	89		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	40		
From 65-84 years	49		
85 years and over			

Gender categorical Units: Subjects			
Female	89		
Male	0		

End points

End points reporting groups	
Reporting group title	Aromatase Inhibitor
Reporting group description: -	
Reporting group title	Metformin
Reporting group description: -	
Reporting group title	Zoledronic acid
Reporting group description: -	
Reporting group title	No treatment
Reporting group description: Randomised to no treatment - standard care at time when trial began	
Reporting group title	AI + Met
Reporting group description: -	
Reporting group title	AI + ZA
Reporting group description: -	
Reporting group title	Met + ZA
Reporting group description: -	
Reporting group title	AI + Met + ZA
Reporting group description: -	
Subject analysis set title	Final IBIS-3
Subject analysis set type	Intention-to-treat
Subject analysis set description: Final analysis of all 89 randomised patients into the IBIS-3 feasibility study.	

Primary: The recruitment of 100 patients within 12 months from first randomisation	
End point title	The recruitment of 100 patients within 12 months from first randomisation
End point description: To determine acceptability and feasibility of recruitment, recruitment rate and number of sites required for main trial.	
End point type	Primary
End point timeframe: 12 months	

End point values	Aromatase Inhibitor	Metformin	Zoledronic acid	No treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	19	16	20
Units: patients	6	19	16	20

End point values	AI + Met	AI + ZA	Met + ZA	AI + Met + ZA
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	4	15	3
Units: patients	6	4	15	3

Statistical analyses

Statistical analysis title	Feasibility study

Statistical analysis description:

For the primary endpoint/outcome there is no formal statistical analysis. The primary outcome was to see whether breast cancer patients can be recruited into this study. All boxes ticked below done so that the form can be saved and closed.

Comparison groups	Aromatase Inhibitor v Metformin v Zoledronic acid v No treatment v AI + Met v AI + ZA v Met + ZA v AI + Met + ZA
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.05
Method	NA
Parameter estimate	NA
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.05
Variability estimate	Standard deviation
Dispersion value	1

Notes:

[1] - For the primary endpoint/outcome there is no formal statistical analysis. The primary outcome was to see whether breast cancer patients can be recruited into this study.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs should be reported from date of randomisation until Last Patient Last Visit (LPLV) plus an additional 14 days if receiving zoledronic acid at final visit.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Aromatase Inhibitor
Reporting group description:	
Patients on AI who reported AE(s)	
Reporting group title	Metformin
Reporting group description:	
Patients on metformin reporting AE(s)	
Reporting group title	Zoledronic acid
Reporting group description: -	
Reporting group title	AI + Met
Reporting group description: -	
Reporting group title	AI + ZA
Reporting group description: -	
Reporting group title	Met + ZA
Reporting group description: -	
Reporting group title	AI + Met + ZA
Reporting group description: -	
Reporting group title	No treatment
Reporting group description: -	

Serious adverse events	Aromatase Inhibitor	Metformin	Zoledronic acid
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	AI + Met	AI + ZA	Met + ZA
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Vascular disorders			
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	AI + Met + ZA	No treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Vascular disorders			
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Aromatase Inhibitor	Metformin	Zoledronic acid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	8 / 19 (42.11%)	8 / 16 (50.00%)
Vascular disorders			
Flushed face			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	1 / 6 (16.67%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Elective knee placement surgery			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Cold sweat			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Discomfort of swollen lymph node			
subjects affected / exposed	0 / 6 (0.00%)	1 / 19 (5.26%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	2 / 19 (10.53%)	5 / 16 (31.25%)
occurrences (all)	1	2	6
Lethargy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 19 (5.26%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Severe fatigue			

subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Urticaria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 19 (5.26%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Vaginal dryness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Flu like symptoms			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	4 / 16 (25.00%)
occurrences (all)	0	0	4
Influenza			
subjects affected / exposed	0 / 6 (0.00%)	1 / 19 (5.26%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Rib pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Feeling low			
subjects affected / exposed	0 / 6 (0.00%)	1 / 19 (5.26%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Mood altered			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood urine present			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			

Fracture of radius			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Dry eye			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 6 (0.00%)	1 / 19 (5.26%)	1 / 16 (6.25%)
occurrences (all)	0	1	2
Parasthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Taste changed			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 19 (5.26%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	1 / 19 (5.26%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Acid reflux (oesophagus)			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Abdominal bloating			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Abdominal pain generalised			
subjects affected / exposed	0 / 6 (0.00%)	1 / 19 (5.26%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Indigestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Indigestion and acid relux			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Loose stools			
subjects affected / exposed	0 / 6 (0.00%)	1 / 19 (5.26%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	3 / 19 (15.79%)	1 / 16 (6.25%)
occurrences (all)	0	3	2
Nausea and vomiting			
subjects affected / exposed	0 / 6 (0.00%)	1 / 19 (5.26%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Oesophagitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Stomach upset			

subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Seborrheic Keratoses			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Urgency of mict			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Aching in limb			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Ankle stiffness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Infusion associated chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Joint stiffness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 19 (5.26%)	0 / 16 (0.00%)
occurrences (all)	0	1	0

Knee pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Muscle and joint pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Other back pain with radiating symptoms			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Right hip pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Shivers			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Stiff neck			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Swollen wrists			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Leg cramps			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Chest infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Infection upper respiratory			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Shingles			

subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Upper respiratory infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Anorexia and bulimia syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 19 (5.26%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Increased thirst			
subjects affected / exposed	0 / 6 (0.00%)	1 / 19 (5.26%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Weight loss			
subjects affected / exposed	0 / 6 (0.00%)	1 / 19 (5.26%)	0 / 16 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	AI + Met	AI + ZA	Met + ZA
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	2 / 4 (50.00%)	9 / 15 (60.00%)
Vascular disorders			
Flushed face			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Hot flush			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Elective knee placement surgery			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Cold sweat			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Discomfort of swollen lymph node			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Lethargy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Severe fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Urticaria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Vaginal dryness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Flu like symptoms			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	2
Influenza			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Rib pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Feeling low			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Mood altered			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood urine present			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Fracture of radius			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Dry eye			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	2 / 15 (13.33%)
occurrences (all)	3	0	2
Parasthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Taste changed			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 6 (100.00%)	0 / 4 (0.00%)	5 / 15 (33.33%)
occurrences (all)	8	0	7
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Acid reflux (oesophagus)			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Abdominal bloating			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	2

Abdominal pain generalised			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Indigestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Indigestion and acid relux			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Loose stools			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	3 / 6 (50.00%)	0 / 4 (0.00%)	6 / 15 (40.00%)
occurrences (all)	3	0	6
Nausea and vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Oesophagitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Stomach upset			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Seborrheic Keratoses			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Urgency of mict			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Aching in limb			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Ankle stiffness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Infusion associated chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Joint stiffness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Knee pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Muscle and joint pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Other back pain with radiating symptoms			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Right hip pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Shivers			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Stiff neck			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Swollen wrists			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Leg cramps			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Chest infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Infection upper respiratory			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Shingles			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Tooth infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Upper respiratory infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0

Metabolism and nutrition disorders			
Anorexia and bulimia syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Increased thirst			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Weight loss			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	AI + Met + ZA	No treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 20 (15.00%)	
Vascular disorders			
Flushed face			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Haemorrhoids			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Hot flush			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Surgical and medical procedures			
Elective knee placement surgery			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Cold sweat			

subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Discomfort of swollen lymph node			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Lethargy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Severe fatigue			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Urticaria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Vaginal dryness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Flu like symptoms			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Rib pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			

Feeling low			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Mood altered			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Investigations			
Blood urine present			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Fracture of radius			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Congenital, familial and genetic disorders			
Dry eye			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Parasthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Taste changed			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Abdominal discomfort			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Acid reflux (oesophagus)			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Abdominal bloating			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Abdominal pain generalised			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Indigestion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Indigestion and acid relux			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Loose stools			

subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Nausea and vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Oesophagitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Stomach upset			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Seborrheic Keratoses			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Urgency of mict			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			

Aching in limb				
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)		
occurrences (all)	0	0		
Ankle stiffness				
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)		
occurrences (all)	0	0		
Infusion associated chills				
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)		
occurrences (all)	0	0		
Joint stiffness				
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)		
occurrences (all)	0	0		
Knee pain				
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)		
occurrences (all)	0	0		
Muscle and joint pain				
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)		
occurrences (all)	0	0		
Other back pain with radiating symptoms				
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)		
occurrences (all)	0	0		
Right hip pain				
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)		
occurrences (all)	0	0		
Shivers				
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)		
occurrences (all)	0	0		
Stiff neck				
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)		
occurrences (all)	0	0		
Swollen wrists				
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)		
occurrences (all)	1	0		
Leg cramps				

subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Chest infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Infection upper respiratory			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Shingles			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Tooth infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Upper respiratory infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Anorexia and bulimia syndrome			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Increased thirst			
subjects affected / exposed	0 / 3 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Decreased appetite			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Weight loss			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 20 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2015	• Update on SAE reporting from the trials unit to the sponsor • Update to TMG membership • Clarification of dose adjustment schedule for Zoledronic acid in the appendix • Update that Completion of CIOMs form is no longer required as it is not a requirement for CTIMPS within the UK • An amendment to clarify PIs can sign SAEs and SUSARs electronically within the app
14 March 2016	• Update membership of the TSC • Change of trial statistician • Removal of reference to long-term follow-up • Clarification of eligibility criteria • Clarification that patients can withdraw from any/all treatments • Request for information on IMP brand and storage requirements to be provided to the trials office • If nurse collects IMP on behalf of patient, a Chain of Custody form should be completed • Clarification that screening blood samples should be taken at same time as research samples; if patients are then deemed ineligible, research blood samples will be kept and stored and may be used for future research • Definition of physical examination and who can perform it • Reference to document providing guidance for nurses on bone health, alcohol and oral hygiene advice • Clarification of type and amounts for blood samples to be collected • Instruction to schedule follow-up appointments 2 weeks before due date • Removal of active 30 day post-treatment SAE reporting • Explanation of how to report SAEs on patients who have stopped treatment • Reference to REC changed to HRA • Clarification that IBIS 3 CCO is within Barts CTU which is part of QMUL and that it is not registered under the Data Protection Act. • Change for removal of plasma to take place at local sites • Information to sites that patient identifiable information should be blacked out from any CRFs or documents when transferring to trials office • Clarification that DMC will meet at least annually rather than every 6 months to be consistent with DMC Charter. • Clarification of when screening ID is allocated, definition of what Patient identifiable information is collected, purpose and how it is stored • Deletion of Study Documents section as not necessary • Clarification that information on screening log is 'pseudoanonymised' rather than 'anonymised'
28 July 2016	• Deletion of text '(Note: death is an outcome and not an event)' to clarify that death is not an outcome and should be reported as an SAE • Clarification of TSC members' roles from 'observers' to 'non-voting members'

21 March 2017	• Allowance of a baseline bone mineral density (BMD) scan to have been done between 12-24 months before joining the trial providing FRAX tool probability of 10 year fracture (%) is estimated and this is defined as low risk. • For baseline DXA scans, explanation that it is acceptable to have hip (femoral neck or proximal femur) OR lumbar spine should T score only be available for one site (due to, for example, prosthesis or artefacts/osteophytes) and the T score for this site is >0. • Allowance of a suitably qualified Advanced Nurse Practitioner to do prescriptions • Recommendation that patients have a dental check-up within 6 months before randomisation in case any dental treatment is required, delaying zoledronic acid treatment. • Addition of 'currently being treated with a bisphosphonate' to exclusion criteria for zoledronic acid • Addition of 'previous intolerance to AIs resulting in unsuitability to extended AI treatment' to exclusion criteria for aromatase inhibitors • Change from date of randomisation to date of screening of timeframe for screening tests • Correction of a typo (CKD-EPI) • Addition that members of the Coordinating Centre may visit hospital sites to assist with screening patients by viewing medical records and databases. • To minimize patient waiting time for IMP and/or additional visits, it was decided that patient does not need to be present for randomisation. Eligibility can be re-checked on the phone before randomisation and within 72 hours of patient visit to collect IMP and complete patient questionnaires.
06 June 2017	• Allowance of a baseline bone mineral density (BMD) scan to have been done between 12-24 months before joining the trial providing FRAX tool probability of 10 year fracture (%) is estimated and this is defined as low risk. • For baseline DXA scans, explanation that it is acceptable to have hip (femoral neck or proximal femur) OR lumbar spine should T score only be available for one site (due to, for example, prosthesis or artefacts/osteophytes) and the T score for this site is >0. • Allowance of a suitably qualified Advanced Nurse Practitioner to do prescriptions • Recommendation that patients have a dental check-up within 6 months before randomisation in case any dental treatment is required, delaying zoledronic acid treatment. • Addition of 'currently being treated with a bisphosphonate' to exclusion criteria for zoledronic acid • Addition of 'previous intolerance to AIs resulting in unsuitability to extended AI treatment' to exclusion criteria for aromatase inhibitors • Change from date of randomisation to date of screening of timeframe for screening tests • Correction of a typo (CKD-EPI) • To minimize patient waiting time for IMP and/or additional visits, it was decided that patient does not need to be present for randomisation. Eligibility can be re-checked on the phone before randomisation and within 72 hours of patient visit to collect IMP and complete patient questionnaires.
27 November 2017	Change of treatment duration from 2 years to 6-18 months (dependent on date of randomisation) • Final visit to be scheduled by 26th March 2018 and end-of-trial blood sample to be collected (as originally planned) • End-of-trial dose of zoledronic acid (ZA) to be administered if previous dose given more than 5 months earlier. The last ZA dose was originally scheduled at 18 months if trial treatment had continued for 24 months (i.e. no ZA dose at the end-of-trial visit). This ensures that all patients randomised to ZA receive the benefit of treatment at last visit. Final visit apppointments for ZA patients should be scheduled for at least 2 weeks before last patient last visit (26th March 2018) as there is a period of 14 days of active pharmacovigilence reporting for these patients. • DXA scan to be done for AI patients who were osteopenic at baseline if the previous scan was more than 12 months ago • Change of TMG members • Change of contact name for sponsor

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The number of patients needed to make a main trial viable was not achieved and the decision was made to terminate earlier than planned but that all patients receive at least 6 months of treatment in order to answer secondary objectives.

Notes: