Clinical trial results:
Influence of Zoledronic acid (Zometa®) on bone mineral density and bone ultrasonometry in premenopausal women with hormone receptor positive breast cancer and neoadjuvant or adjuvant chemotherapeutic treatment

Summary

EudraCT number	2004-002832-24
Trial protocol	DE
Global end of trial date	19 May 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	CZOL446GDE21

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00375505
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 6132411121,

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	19 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 May 2014
Global end of trial reached?	Yes
Global end of trial date	19 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate superiority of Zometa® vs. placebo in improving bone mineral density at lumbar spine (L2-L4) in premenopausal hormone receptor positive patients with breast cancer and neoadjuvant chemotherapy or adjuvant chemoendocrine or endocrine treatment.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	14 October 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 70
Worldwide total number of subjects	70
EEA total number of subjects	70

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)	70
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The patients were either randomized (ratio 1:1) to the placebo or Zometa treatment group, where they received 4 mg ZOL or placebo as an infusion every 3 months (altogether 8 infusions).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo as a 15-minute infusion every 3 months for a treatment period of 24 months (total of 8 infusions).

Arm type	Placebo
Investigational medicinal product name	Matching Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

4 mg ZOL or placebo as an infusion every 3 months (altogether 8 infusions)

Arm title	Zoledronic Acid

Arm description:

Zoledronic Acid 4mg as a 15-minute infusion every 3 months for a treatment period of 24 months (total of 8 infusions).

Arm type	Experimental
Investigational medicinal product name	Zoledronic Acid
Investigational medicinal product code	CZOL446
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

4 mg ZOL or placebo as an infusion every 3 months (altogether 8 infusions)

Number of subjects in period 1	Placebo	Zoledronic Acid
Started	36	34
Completed	35	32
Not completed	1	2
Adverse event, non-fatal	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo as a 15-minute infusion every 3 months for a treatment period of 24 months (total of 8 infusions).	
Reporting group title	Zoledronic Acid
Reporting group description:	
Zoledronic Acid 4mg as a 15-minute infusion every 3 months for a treatment period of 24 months (total of 8 infusions).	

Reporting group values	Placebo	Zoledronic Acid	Total
Number of subjects	36	34	70
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	36	34	70
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous |			
Units: years			
arithmetic mean	42.8	43.2	
standard deviation	± 6.3	± 6	-
Gender, Male/Female			
All participants were females			
Units: participants			
Female	36	34	70
Male	0	0	0

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo as a 15-minute infusion every 3 months for a treatment period of 24 months (total of 8 infusions).	
Reporting group title	Zoledronic Acid
Reporting group description:	
Zoledronic Acid 4mg as a 15-minute infusion every 3 months for a treatment period of 24 months (total of 8 infusions).	

Primary: Change in bone mineral density (BMD) measured by Dual (energy) x-ray absorptiometry (DXA) at lumbar spine (L2-L4) from baseline to month 24

End point title	Change in bone mineral density (BMD) measured by Dual (energy) x-ray absorptiometry (DXA) at lumbar spine (L2-L4) from baseline to month 24
End point description:	
Bone mineral density (BMD) by DXA at lumbar spine (L2-L4); DXA assessments of the BMD at dual hips. (BMD). Two X-ray beams with different energy levels are aimed at the patient's bones. When soft tissue absorption is subtracted out, the BMD can be determined from the absorption of each beam by bone.	
End point type	Primary
End point timeframe:	
baseline, month 24	

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: Z-score				
arithmetic mean (standard deviation)	-0.075 (± 0.041)	0.037 (± 0.042)		

Statistical analyses

Statistical analysis title	Change in BMD
Comparison groups	Placebo v Zoledronic Acid
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA

Primary: Change in bone mineral density (BMD) at lumbar spine (L2-L4) from baseline to month 24 or last visit measure by T-score

End point title	Change in bone mineral density (BMD) at lumbar spine (L2-L4) from baseline to month 24 or last visit measure by T-score

End point description:

Bone mineral density (BMD) at lumbar spine (L2-L4) by T-score. Your T-score is the number of units that your bone density is above or below the average. -1 and above-bone density is considered normal; Between -1 and -2.5-is a sign of osteopenia, a condition in which bone density is below normal and may lead to osteoporosis. -2.5 and below-indicates that it is likely osteoporosis.

End point type	Primary

End point timeframe:

baseline, month 24

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: T-score				
arithmetic mean (standard deviation)	-0.622 (± 0.346)	0.309 (± 0.348)		

Statistical analyses

Statistical analysis title	Change in BMD for T-Score
Comparison groups	Placebo v Zoledronic Acid
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA

Primary: Change in bone mineral density (BMD) at lumbar spine (L2-L4) from baseline to month 24 or last visit measure by Z-score

End point title	Change in bone mineral density (BMD) at lumbar spine (L2-L4) from baseline to month 24 or last visit measure by Z-score

End point description:

Bone mineral density (BMD) at lumbar spine (L2-L4) measured by Z-score. If Z-score is -2 or lower, it may suggest that something other than aging is causing abnormal bone loss.

End point type	Primary

End point timeframe:

baseline, month 24

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: Z-score				
arithmetic mean (standard deviation)	-0.658 (± 0.355)	0.309 (± 0.414)		

Statistical analyses

Statistical analysis title	Change in BMD -Z Score
Comparison groups	Placebo v Zoledronic Acid
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA

Primary: Percent change in bone mineral density for L2-L4 from baseline to month 24 or last visit

End point title	Percent change in bone mineral density for L2-L4 from baseline to month 24 or last visit

End point description:

Bone mineral density (BMD) at lumbar spine (L2-L4) measured by using Lunar or Hologic dual-energy X-ray absorptiometry (DXA) Instruments. Measurements were done in the lumbar vertebrae (L2-L4)

End point type	Primary

End point timeframe:

baseline, month 24

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: percentage change				
arithmetic mean (standard deviation)	6.429 (± 3.414)	3.139 (± 3.388)		

Statistical analyses

Statistical analysis title	Change in BMD - Month 24
Comparison groups	Placebo v Zoledronic Acid

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA

Secondary: Change in bone mineral density for femoral neck (right and left side) from baseline to month 24

End point title	Change in bone mineral density for femoral neck (right and left side) from baseline to month 24

End point description:

Bone mineral density (BMD) for femoral neck (right and left side) is measured by using Lunar or Hologic dual-energy X-ray absorptiometry (DXA) Instruments. Measurements were done on femoral neck (right and left side)

End point type	Secondary

End point timeframe:

baseline, month 24

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: change in BMD				
arithmetic mean (standard deviation)				
femoral neck (right)	-0.023 (± 0.033)	0.011 (± 0.021)		
femoral neck (left)	-0.023 (± 0.035)	0.008 (± 0.028)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in bone mineral density for total femoral neck (right and left side) from baseline to month 24

End point title	Change in bone mineral density for total femoral neck (right and left side) from baseline to month 24

End point description:

Bone mineral density (BMD) for total femoral neck (right and left side) is measured by using Lunar or Hologic dual-energy X-ray absorptiometry (DXA) Instruments. Measurements were done on femoral neck (right and left side)

End point type	Secondary

End point timeframe:

baseline, month 24

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: change in BMD				
arithmetic mean (standard deviation)				
femoral neck (right)	-0.039 (± 0.028)	0.013 (± 0.018)		
femoral neck (left)	-0.036 (± 0.028)	0.014 (± 0.018)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in bone mineral density Os calcis (right and left side) from baseline to month 24 as measured by speed of sound (SOS)

End point title	Change in bone mineral density Os calcis (right and left side) from baseline to month 24 as measured by speed of sound (SOS)

End point description:

Bone mineral density (BMD) for Os calcis (right and left side) is measured by SOS; SOS is a Quantitative ultrasonography scanning and measures bone mass and strength and assesses bone microarchitecture by detecting the transmission of high-frequency sound waves through bone.

End point type	Secondary

End point timeframe:

baseline, month 24

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: m/s				
arithmetic mean (standard deviation)				
Os calcis (right)	-13.139 (± 23.111)	-10.853 (± 16.613)		
Os calcis (left)	-13.028 (± 19.761)	-13.485 (± 15.969)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in bone mineral density Os calcis (right and left side) from

baseline to month 24 as measured by broadband ultrasound attenuation (BUA)

End point title	Change in bone mineral density Os calcis (right and left side) from baseline to month 24 as measured by broadband ultrasound attenuation (BUA)

End point description:

Bone mineral density (BMD) for Os calcis (right and left side) is measured by BUA; BUA is a Quantitative ultrasonography scanning and measures bone mass and strength and assesses bone microarchitecture by detecting the transmission of high-frequency sound waves through bone.

End point type	Secondary

End point timeframe:

baseline, month 24

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: dB/MHz				
arithmetic mean (standard deviation)				
Os calcis (right)	-0.306 (± 11.369)	1.824 (± 8.997)		
Os calcis (left)	-2.417 (± 12.514)	1.848 (± 9.628)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in bone mineral density Phalanges II, III, IV, and V from baseline to month 24 or last visit as measured by Amplitude-dependent speed of sound (ADSOS)

End point title	Change in bone mineral density Phalanges II, III, IV, and V from baseline to month 24 or last visit as measured by Amplitude-dependent speed of sound (ADSOS)

End point description:

Bone mineral density (BMD) for Phalanges II, III, IV, and V is measured by ADSOS; ADSOS is a Quantitative ultrasonography scanning and measures bone mass and strength and assesses bone microarchitecture by detecting the transmission of high-frequency sound waves through bone.

End point type	Secondary

End point timeframe:

baseline, month 24

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: m/s				
arithmetic mean (standard deviation)				
Phalanges II (n=35, 33)	-48.514 (± 50.905)	-21.485 (± 78.284)		
Phalanges III (n=35, 33)	-62.971 (± 53.76)	-19.879 (± 70.968)		
Phalanges IV (n=35, 33)	-49.086 (± 61.99)	0.455 (± 93.598)		
Phalanges V (n=35, 33)	-35 (± 38.072)	0.303 (± 79.985)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Serum CTX-carboxy-terminal collagen crosslinks from baseline to month 24

End point title	Change in Serum CTX-carboxy-terminal collagen crosslinks from baseline to month 24

End point description:

CTX is a telopeptide that can be used as a biomarker in the serum to measure the rate of bone turnover. The test used to detect the CTX marker is specific to bone resorption.

End point type	Secondary

End point timeframe:

baseline, month 24

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: ng/mL				
arithmetic mean (standard deviation)	0.137 (± 0.164)	-0.118 (± 0.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Aminoterminal propeptide on type I procollagen (P1NP) from baseline to month 24

End point title	Change in Aminoterminal propeptide on type I procollagen (P1NP) from baseline to month 24

End point description:

Change in Aminoterminal propeptide on type I procollagen (P1NP) from baseline to month 24. P1NP is a

marker for bone formation. It is a specific indicator of type 1 collagen deposition. P1NP is increased in states of high bone turnover

End point type	Secondary

End point timeframe:

baseline, month 24

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: ng/ml				
arithmetic mean (standard deviation)	16.729 (± 19.346)	-21.476 (± 13.142)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Estradiol (E2) from baseline to month 24

End point title	Change in Estradiol (E2) from baseline to month 24

End point description:

Change in Estradiol from baseline to month 24

End point type	Secondary

End point timeframe:

baseline, month 24

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: ng/L				
arithmetic mean (standard deviation)	-119.026 (± 213.03)	-10.421 (± 134.529)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Follicle- Stimulating Hormone (FSH) from baseline to month 24

End point title	Change in Follicle- Stimulating Hormone (FSH) from baseline to month 24

End point description:

Change in Follicle- Stimulating Hormone (FSH) from baseline to month 24

End point type	Secondary
End point timeframe: baseline, month 24	

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: mIU/ml				
arithmetic mean (standard deviation)	-0.593 (± 36.851)	0.86 (± 28.444)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Testosterone from baseline to month 24

End point title	Change in Testosterone from baseline to month 24
End point description: Change in Testosterone from baseline to month 24	
End point type	Secondary
End point timeframe: baseline, month 24	

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: ng/ml				
arithmetic mean (standard deviation)	0.039 (± 0.11)	0.015 (± 0.111)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Sex Hormone binding globulin (SHGB) from baseline to month 24

End point title	Change in Sex Hormone binding globulin (SHGB) from baseline to month 24
End point description: Change in Sex Hormone binding globulin (SHGB) from baseline to month 24	
End point type	Secondary

End point timeframe:
baseline, month 24

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: nmol/l				
arithmetic mean (standard deviation)	5.609 (± 45.614)	12.806 (± 32.501)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Parathyroid Hormone (PTH) from baseline to month 24

End point title	Change in Parathyroid Hormone (PTH) from baseline to month 24

End point description:
Change in Parathyroid Hormone (PTH) from baseline to month 24

End point type	Secondary

End point timeframe:
baseline, month 24

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: pg/ml				
arithmetic mean (standard deviation)	7.288 (± 12.838)	4.729 (± 10.401)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Vitamine D from baseline to month 24

End point title	Change in Vitamine D from baseline to month 24

End point description:
Change in Vitamine D from baseline to month 24

End point type	Secondary

End point timeframe:
baseline, month 24

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: ng/ml				
arithmetic mean (standard deviation)	11.163 (± 9.234)	9.638 (± 9.242)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in anti-Mueller hormone (AMH) from baseline to month 24

End point title	Change in anti-Mueller hormone (AMH) from baseline to month 24
End point description: Change in anti-Mueller hormone (AMH) from baseline to month 24	
End point type	Secondary
End point timeframe: baseline, month 24	

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: ng/ml				
arithmetic mean (standard deviation)	-0.584 (± 0.962)	-0.878 (± 2.019)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Inhibin A and Inhibin B from baseline to month 24

End point title	Change in Inhibin A and Inhibin B from baseline to month 24
End point description: Change in Inhibin A and Inhibin B from baseline to month 24	
End point type	Secondary
End point timeframe: baseline, month 24	

End point values	Placebo	Zoledronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: pg/ml				
arithmetic mean (standard deviation)				
Inhibin A (n=34,34)	-19.079 (± 29.592)	-10.209 (± 24.125)		
Inhibin B (n=34,34)	-28.2 (± 41.545)	-39.126 (± 43.421)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	Zometa

Reporting group description:

Zometa

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	Zometa	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 34 (17.65%)	3 / 36 (8.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BREAST CANCER			
subjects affected / exposed	1 / 34 (2.94%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOMA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
ADENOIDECTOMY			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

HYSTERECTOMY			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
ATAXIA			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
DENTAL CARIES			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL OEDEMA			

subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOCHEZIA			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
MENORRHAGIA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
OSTEONECROSIS			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
FEBRILE INFECTION			

subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBCUTANEOUS ABSCESS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Zometa	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 34 (97.06%)	36 / 36 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	16 / 34 (47.06%)	20 / 36 (55.56%)	
occurrences (all)	16	20	
HYPERTENSION			
subjects affected / exposed	2 / 34 (5.88%)	3 / 36 (8.33%)	
occurrences (all)	2	3	
LYMPHOEDEMA			
subjects affected / exposed	11 / 34 (32.35%)	19 / 36 (52.78%)	
occurrences (all)	11	20	
THROMBOSIS			
subjects affected / exposed	1 / 34 (2.94%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
CHILLS			
subjects affected / exposed	7 / 34 (20.59%)	1 / 36 (2.78%)	
occurrences (all)	9	1	
FATIGUE			

subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
IMPAIRED HEALING			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	11 / 34 (32.35%)	4 / 36 (11.11%)	
occurrences (all)	11	5	
PYREXIA			
subjects affected / exposed	3 / 34 (8.82%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
Reproductive system and breast disorders			
MENOPAUSAL SYMPTOMS			
subjects affected / exposed	16 / 34 (47.06%)	14 / 36 (38.89%)	
occurrences (all)	16	14	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	2 / 34 (5.88%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	5 / 34 (14.71%)	1 / 36 (2.78%)	
occurrences (all)	5	1	
SLEEP DISORDER			
subjects affected / exposed	2 / 34 (5.88%)	7 / 36 (19.44%)	
occurrences (all)	2	7	
Investigations			
HEPATIC ENZYME INCREASED			
subjects affected / exposed	3 / 34 (8.82%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
Injury, poisoning and procedural complications			
RADIATION SKIN INJURY			
subjects affected / exposed	2 / 34 (5.88%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			

HEADACHE			
subjects affected / exposed	6 / 34 (17.65%)	3 / 36 (8.33%)	
occurrences (all)	8	3	
MIGRAINE			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
MOVEMENT DISORDER			
subjects affected / exposed	2 / 34 (5.88%)	3 / 36 (8.33%)	
occurrences (all)	2	3	
PARAESTHESIA			
subjects affected / exposed	4 / 34 (11.76%)	6 / 36 (16.67%)	
occurrences (all)	4	6	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 34 (0.00%)	3 / 36 (8.33%)	
occurrences (all)	0	3	
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
LEUKOPENIA			
subjects affected / exposed	2 / 34 (5.88%)	4 / 36 (11.11%)	
occurrences (all)	2	4	
Eye disorders			
VISUAL IMPAIRMENT			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
ABDOMINAL PAIN UPPER			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
CONSTIPATION			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
GASTRITIS			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
NAUSEA			

subjects affected / exposed	8 / 34 (23.53%)	5 / 36 (13.89%)	
occurrences (all)	8	6	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	1 / 34 (2.94%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
HYPERHIDROSIS			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Renal and urinary disorders			
URGE INCONTINENCE			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	16 / 34 (47.06%)	22 / 36 (61.11%)	
occurrences (all)	16	26	
BACK PAIN			
subjects affected / exposed	4 / 34 (11.76%)	4 / 36 (11.11%)	
occurrences (all)	4	4	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	2 / 34 (5.88%)	2 / 36 (5.56%)	
occurrences (all)	2	2	
BONE PAIN			
subjects affected / exposed	11 / 34 (32.35%)	12 / 36 (33.33%)	
occurrences (all)	12	16	
MUSCULOSKELETAL STIFFNESS			
subjects affected / exposed	1 / 34 (2.94%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
MYALGIA			
subjects affected / exposed	5 / 34 (14.71%)	0 / 36 (0.00%)	
occurrences (all)	7	0	
PAIN IN EXTREMITY			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
OSTEOARTHRITIS			

subjects affected / exposed	1 / 34 (2.94%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
PAIN IN JAW			
subjects affected / exposed	2 / 34 (5.88%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	4 / 34 (11.76%)	1 / 36 (2.78%)	
occurrences (all)	5	1	
CYSTITIS			
subjects affected / exposed	2 / 34 (5.88%)	3 / 36 (8.33%)	
occurrences (all)	2	4	
GASTROENTERITIS			
subjects affected / exposed	1 / 34 (2.94%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
MASTITIS			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
INFLUENZA			
subjects affected / exposed	3 / 34 (8.82%)	2 / 36 (5.56%)	
occurrences (all)	4	2	
TOOTH ABSCESS			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
VAGINAL INFECTION			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
VULVOVAGINAL CANDIDIASIS			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
HYPOKALAEMIA			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2006	Issued after the inclusion of the first patient, introduced the following changes: - Change on Inclusion criteria 2: deletion of absence of evidence of regional lymph node metastasis (N0) Patient is premenopausal at diagnosis of breast cancer (spontaneous and regular - Change on Inclusion criteria 6: correction of estradiol level unit in > 10 ng/ml - Clarification of randomization, treatment blinding and medication procedure- Patients can receive adjuvant chemotherapy but do not have to.
11 December 2006	Issued after the inclusion of the first patient, introduced the following changes: Inclusion criteria: Patients under adjuvant chemoendocrine or endocrine therapy: Node negative (pN-) and Node positive (pN+; ≤ 4 positive lymph nodes) patients - Inclusion criteria: Patients under neoadjuvant chemotherapy: no clinical evidence for nodal involvement -Inclusion criteria: Patient is premenopausal; determined by spontaneous and regular menses at diagnosis of breast cancer or by premenopausal estradiol levels (>20ng/L) at diagnosis of breast cancer - Clarification of ONJ cases
23 November 2007	Issued after the inclusion of the first patient, introduced the following changes: - Change in secondary objective: Development of metastases as assessed by X-ray, CT, bone scan or MRI during 24 months and during 60 months, if data available - Change in assessment at final visit/month 60: Tumor assessments will be performed to exclude presence of bone metastases only if clinically indicated
28 November 2008	Issued after the inclusion of the first patient, introduced the following changes: - BMD by DXA and QUS as well as Tumor Assessments do not have to be repeated at Baseline (-1 month to 0) if recent data from assessments within 12 weeks to Randomization (-3 months to 0) are available and reduction of BMD and progression of disease is not suspected
29 June 2011	Issued after the inclusion of the first patient, introduced the following changes: - Change in secondary objective/efficacy assessments: additional analysis of the following biochemical markers: CTX PTH, SHBG, Testosterone, Vitamine D, anti-Müller-Hormone (AMH), Inhibin A/B, Activin A, OPG, RANKL, BSP, Sclerostin and DKK-1. Deletion of the following markers: osteocalcin, deoxypyridinoline in serum.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported