Clinical trial results:
A randomized, multicenter, open phase III study comparing the postoperative use of zoledronic acid versus no treatment in patients with histological tumor residuals after preoperative anthracycline and taxane containing chemotherapy for primary breast cancer (NEO-ADJUVANT TRIAL ADD-ON)

Summary

EudraCT number	2004-002355-14
Trial protocol	DE AT
Global end of trial date	13 December 2013

Results information

Result version number	v1 (current)
This version publication date	27 January 2023
First version publication date	27 January 2023
Summary attachment (see zip file)	CSR Synopsis (NaTaN_CSR_2.0_synopsis_signed.pdf)

Trial information

Trial identification

Sponsor protocol code	GBG36

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00512993
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GBG Forschungs GmbH
Sponsor organisation address	Martin-Behaim-Straße 12, Neu-Isenburg, Germany, 63263
Public contact	Medicine and Research, GBG Forschungs GmbH, publications@gbg.de
Scientific contact	Medicine and Research, GBG Forschungs GmbH, publications@gbg.de

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	05 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess disease-free survival (DFS) after zoledronate given for 5 years versus no postoperative treatment in patients with invasive residual breast cancer (ypT1-4 and/or ypN1-3) after preoperative anthracycline/taxane containing chemotherapy.
Of note, DFS was called event-free survival (EFS) in the study protocol.

Protection of trial subjects:

The trial protocol including amendments, the patient information and the informed consent were reviewed and approved from a properly constituted IRB/IEC for each site prior to the study start. The trial was in compliance with the International Conference on Harmonization (ICH) - Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (E6), and the Commission Directives in the European Community as well as with the applicable German national laws and regulations, and with Declaration of Helsinki and its revisions in all aspects of preparation, monitoring, reporting, auditing, and archiving.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	19 January 2005
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	Austria: 24
Country: Number of subjects enrolled	Germany: 655
Worldwide total number of subjects	679
EEA total number of subjects	679

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)	596
From 65 to 84 years	83
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 87 centers in Germany and Austria.

Pre-assignment

Screening details:

Patients with invasive residual breast cancer (ypT1-4 and/or ypN1-3) after preoperative anthracycline/taxane containing chemotherapy.

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?	Yes
Arm title	Zoledronate

Arm description:

329 patients with invasive residual breast cancer (ypT1-4 and/or ypN1-3) after preoperative anthracycline/taxane-containing chemotherapy received zoledronate 4 mg i.v. for 5 years

Arm type	Experimental
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	Zoledronic acid, Zoledronate
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Zoledronate 4 mg i.v. for 5 years. Zoledronate was given every 4 weeks for the first 6 months, every 3 months the following 2 years, and every 6
months for the last 2.5 years.

Investigational medicinal product name	Calcium and Vitamin D
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

Calcium and Vitamin D (as supplement, if applicable)

Arm title	Observation

Arm description:

350 patients with invasive residual breast cancer (ypT1-4 and/or ypN1-3) after preoperative anthracycline/taxane-containing chemotherapy who did not receive postoperative bisphosphonate treatment

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Zoledronate	Observation
Started	329	350
Completed	179	350
Not completed	150	0
death	7	-
Adverse event, non-fatal	10	-
patient wish	28	-
Unknown	35	-
Lost to follow-up	5	-
disease progression	65	-

Baseline characteristics

Reporting groups	
Reporting group title	Zoledronate
Reporting group description:	
329 patients with invasive residual breast cancer (ypT1-4 and/or ypN1-3) after preoperative anthracycline/taxane-containing chemotherapy received zoledronate 4 mg i.v. for 5 years	
Reporting group title	Observation
Reporting group description:	
350 patients with invasive residual breast cancer (ypT1-4 and/or ypN1-3) after preoperative anthracycline/taxane-containing chemotherapy who did not receive postoperative bisphosphonate treatment	

Reporting group values	Zoledronate	Observation	Total
Number of subjects	329	350	679
Age categorical			
Units: Subjects			
Adults (18-64 years)	291	305	596
From 65-84 years	38	45	83
Age continuous			
age at randomization, years			
Units: years			
median	50	50	
standard deviation	± 9.9	± 9.9	-
Gender categorical			
Units: Subjects			
Female	329	350	679
Male	0	0	0

End points

End points reporting groups

Reporting group title	Zoledronate
Reporting group description:	
329 patients with invasive residual breast cancer (ypT1-4 and/or ypN1-3) after preoperative anthracycline/taxane-containing chemotherapy received zoledronate 4 mg i.v. for 5 years	
Reporting group title	Observation
Reporting group description:	
350 patients with invasive residual breast cancer (ypT1-4 and/or ypN1-3) after preoperative anthracycline/taxane-containing chemotherapy who did not receive postoperative bisphosphonate treatment	

Primary: DFS

End point title	DFS
End point description:	
DFS was defined as the time in months between the randomization and any event, i.e. invasive or non-invasive ipsilateral locoregional, contralateral, distant recurrence, secondary primaries or death due to any cause (corresponding to DFS-DCIS). Overall survival (OS) was defined as the interval between the date of randomization and the date of death due to any cause. Patients without documented event were censored at the date of the last contact. Of note, DFS was called event-free survival (EFS) in the study protocol.	
End point type	Primary
End point timeframe:	
5 years.	

End point values	Zoledronate	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	329	350		
Units: events	82	87		

Statistical analyses

Statistical analysis title	DFS
Comparison groups	Zoledronate v Observation
Number of subjects included in analysis	679
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.789
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occurring during the treatment period were reported.

Adverse event reporting additional description:

AEs are reported per patient during the complete treatment duration for the overall safety population (N=467). Note, overall number of single AE occurrences per term was not assessed, only per patient

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	0

Reporting groups

Reporting group title	Observation
Reporting group description: -	
Reporting group title	Zoledronate
Reporting group description:	
zoledronate 4 mg i.v. for 5 years	

Serious adverse events	Observation	Zoledronate	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 239 (8.79%)	60 / 228 (26.32%)	
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)			
Myeloid leukaemia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign breast neoplasm			
subjects affected / exposed	1 / 239 (0.42%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma of breast			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian adenoma			

subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspicion of metastases			
subjects affected / exposed	0 / 239 (0.00%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cognitive disturbance			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Collapse			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 239 (0.00%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotesia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			

subjects affected / exposed	1 / 239 (0.42%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Colon polypectomy			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Premature labour			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (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			
General disorder			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic pain			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
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			
Fallopian tube cyst			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cardiopulmonary arrest			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	0 / 239 (0.00%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fear of disease			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture	Additional description: Arm fracture		
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus lesion			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accident	Additional description: Road traffic accident		
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Unspecific injury			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Vestibular disorder			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weakness			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Epigastric discomfort			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small bowel obstruction			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Calculous cholecystitis			

subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pain back			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arnold-Chiari malformation			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthrosis	Additional description: Arthrosis NOS		
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar disc herniation			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteonecrosis of jaw			
subjects affected / exposed	0 / 239 (0.00%)	5 / 228 (2.19%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in arm			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prolapsed lumbar disc			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Allergy			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			

subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cold			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 239 (0.42%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	1 / 239 (0.42%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	0 / 239 (0.00%)	1 / 228 (0.44%)	
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	Observation	Zoledronate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	179 / 239 (74.90%)	197 / 228 (86.40%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign			
subjects affected / exposed	6 / 239 (2.51%)	5 / 228 (2.19%)	
occurrences (all)	6	5	
Vascular disorders			
other Vascular disorders			
subjects affected / exposed	39 / 239 (16.32%)	36 / 228 (15.79%)	
occurrences (all)	39	36	
Hot flushes			
subjects affected / exposed	49 / 239 (20.50%)	49 / 228 (21.49%)	
occurrences (all)	49	49	
Oedema			
subjects affected / exposed	27 / 239 (11.30%)	31 / 228 (13.60%)	
occurrences (all)	27	31	
Surgical and medical procedures			
Surgical and medical prosedures			
subjects affected / exposed	4 / 239 (1.67%)	8 / 228 (3.51%)	
occurrences (all)	4	8	
General disorders and administration site conditions			
Fever without neutropenia			
subjects affected / exposed	1 / 239 (0.42%)	28 / 228 (12.28%)	
occurrences (all)	1	28	
Fatigue			
subjects affected / exposed	36 / 239 (15.06%)	65 / 228 (28.51%)	
occurrences (all)	36	65	
Pain NOS			

subjects affected / exposed	18 / 239 (7.53%)	21 / 228 (9.21%)	
occurrences (all)	18	21	
Other general disorders			
subjects affected / exposed	2 / 239 (0.84%)	16 / 228 (7.02%)	
occurrences (all)	2	16	
Immune system disorders			
Immune system disorders			
subjects affected / exposed	4 / 239 (1.67%)	7 / 228 (3.07%)	
occurrences (all)	4	7	
Reproductive system and breast disorders			
Other reproductive system disorders			
subjects affected / exposed	27 / 239 (11.30%)	23 / 228 (10.09%)	
occurrences (all)	27	23	
Respiratory, thoracic and mediastinal disorders			
Respiratory			
subjects affected / exposed	25 / 239 (10.46%)	28 / 228 (12.28%)	
occurrences (all)	25	28	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	31 / 239 (12.97%)	30 / 228 (13.16%)	
occurrences (all)	31	30	
Investigations			
Investigations			
subjects affected / exposed	1 / 239 (0.42%)	1 / 228 (0.44%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	9 / 239 (3.77%)	12 / 228 (5.26%)	
occurrences (all)	9	12	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	8 / 239 (3.35%)	11 / 228 (4.82%)	
occurrences (all)	8	11	
Nervous system disorders			
Sensory neuropathy			

subjects affected / exposed	31 / 239 (12.97%)	46 / 228 (20.18%)	
occurrences (all)	31	46	
Other neurological disorders			
subjects affected / exposed	19 / 239 (7.95%)	32 / 228 (14.04%)	
occurrences (all)	19	32	
Headache			
subjects affected / exposed	13 / 239 (5.44%)	19 / 228 (8.33%)	
occurrences (all)	13	19	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	13 / 239 (5.44%)	14 / 228 (6.14%)	
occurrences (all)	13	14	
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	4 / 239 (1.67%)	2 / 228 (0.88%)	
occurrences (all)	4	2	
Eye disorders			
Eye disorders			
subjects affected / exposed	12 / 239 (5.02%)	16 / 228 (7.02%)	
occurrences (all)	12	16	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	39 / 239 (16.32%)	61 / 228 (26.75%)	
occurrences (all)	39	61	
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	13 / 239 (5.44%)	13 / 228 (5.70%)	
occurrences (all)	13	13	
Skin and subcutaneous tissue disorders			
Other skin and subcutaneous tissues disorders			
subjects affected / exposed	26 / 239 (10.88%)	42 / 228 (18.42%)	
occurrences (all)	26	42	
Alopecia			
subjects affected / exposed	18 / 239 (7.53%)	23 / 228 (10.09%)	
occurrences (all)	18	23	
Renal and urinary disorders			

Renal and urinary disorders			
subjects affected / exposed	4 / 239 (1.67%)	7 / 228 (3.07%)	
occurrences (all)	4	7	
Endocrine disorders			
Endocrine disorders			
subjects affected / exposed	6 / 239 (2.51%)	3 / 228 (1.32%)	
occurrences (all)	6	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	54 / 239 (22.59%)	63 / 228 (27.63%)	
occurrences (all)	54	63	
Bone pain			
subjects affected / exposed	41 / 239 (17.15%)	62 / 228 (27.19%)	
occurrences (all)	41	62	
Other musculo-skeletal disorders			
subjects affected / exposed	48 / 239 (20.08%)	48 / 228 (21.05%)	
occurrences (all)	48	48	
Myalgia			
subjects affected / exposed	10 / 239 (4.18%)	29 / 228 (12.72%)	
occurrences (all)	10	29	
Back pain			
subjects affected / exposed	12 / 239 (5.02%)	19 / 228 (8.33%)	
occurrences (all)	12	19	
Infections and infestations			
Infection			
subjects affected / exposed	40 / 239 (16.74%)	53 / 228 (23.25%)	
occurrences (all)	40	53	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	26 / 239 (10.88%)	15 / 228 (6.58%)	
occurrences (all)	26	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2005	Amendment 1 of the study protocol (version 2 from 01.12.2005) included the following changes: - Inclusion for postneoadjuvant treatment for all prior neoadjuvant patients (not only study patients as add on to neoadjuvant protocol) - Letrozole could be given only to menopausal women older than 50 years. Use not mandatory within the study, only highly recommended - Dose reduction scheme for zolendronic acid for patients with reduced renal function - Exclusion of patients with a history of dental problems (infection of the teeth or jawbone [maxilla or mandibular]; dental or fixture trauma, or a current or prior diagnosis of osteonecrosis of the jaw, of exposed bone in the mouth, or of slow healing after dental procedures).
15 June 2007	Amendment 2 of the study protocol (version 3 from 15.06.2007) included the following changes: - The study design/methodology was amended to multinational trial conducted in cooperation with the Austrian Breast & Colorectal Cancer Study Group (ABCSG) - Patients with ypT1-4 were also eligible - In the rational of the trial, participation in a preoperative chemotherapy trial investigating anthracycline and taxan based regimen was allowed, but not mandatory for all patients - Primary objective was modified as follows: to determine the disease-free survival (DFS)* after zoledronic acid for 5 years versus no postoperative treatment in patients with invasive residual breast cancer (ypT1-4 and/or ypN1-3) after preoperative anthracycline/taxane containing chemotherapy - The dose of vitamin D used as premedication or supportive therapy was increased to 880 I.U - Statistical considerations were changed as follows: a 5-year DFS* rate of 67.2% was expected in the zoledronate arm corresponding to a hazard ratio of 0.73. A two-sided log-rank test was planned with a α 5%, 1-ß of 80%, and an exponential drop-out rate of 5% over an accrual period of 48 months and a followup period of 48 months. To compare proportional hazards without covariates 316 DFS events from 654 randomised patients were needed (section 9.1 of the CSR) - An interim analysis for efficacy with adjusted alpha was planned after 158 events were observed - After the development of bone metastases, patients of both arms should receive bisphosphonates according to local treatment guidelines - Changes in the administrative structure

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27323347