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

Summary

EudraCT number	2004-002831-14
Trial protocol	DE
Global end of trial date	02 December 2013

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	CZOL446GDE13

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00333229
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 613241111,

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	02 December 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 December 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary Objective: to demonstrate superiority of Zometa® vs. placebo in improving bone mineral density at lumbar spine (L2-L4) in premenopausal hormone receptor negative patients with breast cancer and neoadjuvant or adjuvant chemotherapeutic 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	22 March 2006
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: 11
Worldwide total number of subjects	11
EEA total number of subjects	11

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)	11
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

11 patients were enrolled in the study. The safety and the ITT population consisted of 11 patients. In total 11 patients were treated in the study.

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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Zoledronic Acid

Arm description:

Patients randomized into the Zometa arm received a total of 8 study drug infusions which were applied every 3 months. Patients received treatment for 24 months every 3 months.

Arm type	Experimental
Investigational medicinal product name	Zoledronic Acid
Investigational medicinal product code	ZOL446
Other name	Zometa®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

4 mg Zoledronic acid in 5 mL concentrate solutioninfusion every 3 months for 24 months

Arm title	Placebo

Arm description:

Patients randomized into the Placebo Arm received a total of 8 placebo infusions which were applied every 3 months. Patients received treatment for 24 months every 3 months.

Arm type	Experimental
Investigational medicinal product name	Placebo to Zoledronic Acid
Investigational medicinal product code	ZOL446
Other name	Placebo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo to match Zoledronic acid in 5 mL concentrate solutioninfusion every 3 months for 24 months

Number of subjects in period 1	Zoledronic Acid	Placebo
Started	6	5
Completed	6	4
Not completed	0	1
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Zoledronic Acid
Reporting group description:	
Patients randomized into the Zometa arm received a total of 8 study drug infusions which were applied every 3 months. Patients received treatment for 24 months every 3 months.	
Reporting group title	Placebo
Reporting group description:	
Patients randomized into the Placebo Arm received a total of 8 placebo infusions which were applied every 3 months. Patients received treatment for 24 months every 3 months.	

Reporting group values	Zoledronic Acid	Placebo	Total
Number of subjects	6	5	11
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)	6	5	11
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous | Units: Years			
arithmetic mean	41.2	43.2	
standard deviation	± 6.2	± 2.6	-
Gender, Male/Female Units: Participants			
Female	6	5	11
Male	0	0	0

End points

End points reporting groups

Reporting group title	Zoledronic Acid

Reporting group description:

Patients randomized into the Zometa arm received a total of 8 study drug infusions which were applied every 3 months. Patients received treatment for 24 months every 3 months.

Reporting group title	Placebo

Reporting group description:

Patients randomized into the Placebo Arm received a total of 8 placebo infusions which were applied every 3 months. Patients received treatment for 24 months every 3 months.

Primary: Change in bone mineral density (BMD) measured by DXA at lumbar spine (L2-L4) between baseline and 24 months.

End point title	Change in bone mineral density (BMD) measured by DXA at lumbar spine (L2-L4) between baseline and 24 months.[1]

End point description:

"No statistical analysis was planned for this primary outcome."

End point type	Primary

End point timeframe:

24 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical Analasis as study was terminated due to slow recruitment. Sample size could not be achieved and the study was terminated after enrolling only 11 patients.

End point values	Zoledronic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: BMD				
number (not applicable)				

Notes:

[2] - terminated no data to present

[3] - terminated no data to present

Statistical analyses

No statistical analyses for this end point

Secondary: Bone mineral density (BMD) measured by QUS at os calcis and phalanges after 24 months

End point title	Bone mineral density (BMD) measured by QUS at os calcis and phalanges after 24 months

End point description:

End point type	Secondary

End point timeframe:

2 years

End point values	Zoledronic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: BMD				
number (not applicable)				

Notes:

[4] - terminated no data to present

[5] - terminated no data to present

Statistical analyses

No statistical analyses for this end point

Secondary: Course of biochemical markers of bone turn over (FSH, estradiol (E2), osteocalcin, PINP, procollagene-I-peptid, deoxypyridinoline in serum)

End point title	Course of biochemical markers of bone turn over (FSH, estradiol (E2), osteocalcin, PINP, procollagene-I-peptid, deoxypyridinoline in serum)

End point description:

End point type	Secondary

End point timeframe:

2 years

End point values	Zoledronic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: BMD				
number (not applicable)				

Notes:

[6] - terminated no data to present

[7] - terminated no data to present

Statistical analyses

No statistical analyses for this end point

Secondary: Pathologic fractures during 24 month

End point title	Pathologic fractures during 24 month

End point description:

End point type	Secondary

End point timeframe:

2 years

End point values	Zoledronic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: number of fractures				
number (not applicable)				

Notes:

[8] - terminated no data to present

[9] - terminated no data to present

Statistical analyses

No statistical analyses for this end point

Secondary: Development of metastases as assessed by X-ray, CT, or MRI during 24 months and during 60 months

End point title	Development of metastases as assessed by X-ray, CT, or MRI during 24 months and during 60 months

End point description:

End point type	Secondary

End point timeframe:

2 years

End point values	Zoledronic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: number of metastases				
number (not applicable)				

Notes:

[10] - terminated no data to present

[11] - terminated no data to present

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

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	1 / 6 (16.67%)	1 / 5 (20.00%)	
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)			
BENIGN BREAST NEOPLASM			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
VISUAL IMPAIRMENT			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
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	6 / 6 (100.00%)	5 / 5 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MELANOCYTIC NAEVUS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
THYROID NEOPLASM			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	2 / 6 (33.33%)	2 / 5 (40.00%)	
occurrences (all)	2	2	
LYMPHOEDEMA			
subjects affected / exposed	5 / 6 (83.33%)	3 / 5 (60.00%)	
occurrences (all)	5	3	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
CHEST PAIN			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
MUCOSAL DRYNESS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	

PAIN			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
MENOPAUSAL SYMPTOMS			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
POSTMENOPAUSAL HAEMORRHAGE			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
UTERINE POLYP			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
DYSPHONIA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
OROPHARYNGEAL PAIN			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
CONVERSION DISORDER			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
DEPRESSION			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
SLEEP DISORDER			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
Investigations			
HEPATIC ENZYME INCREASED			

subjects affected / exposed	1 / 6 (16.67%)	2 / 5 (40.00%)	
occurrences (all)	1	2	
Nervous system disorders			
AMNESIA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
HEADACHE			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
PARAESTHESIA			
subjects affected / exposed	2 / 6 (33.33%)	3 / 5 (60.00%)	
occurrences (all)	2	5	
SYNCOPE			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
TINNITUS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
VERTIGO			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
DRY EYE			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
DYSPEPSIA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
GASTRITIS			

subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
HAEMORRHOIDS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
NAUSEA			
subjects affected / exposed	2 / 6 (33.33%)	2 / 5 (40.00%)	
occurrences (all)	2	2	
Hepatobiliary disorders			
HEPATIC STEATOSIS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
AUTOIMMUNE THYROIDITIS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	3 / 6 (50.00%)	3 / 5 (60.00%)	
occurrences (all)	4	3	
BACK PAIN			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
BONE PAIN			
subjects affected / exposed	3 / 6 (50.00%)	2 / 5 (40.00%)	
occurrences (all)	5	3	
MYALGIA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
MYOSCLEROSIS			

subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
OSTEOCHONDROSIS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
RHEUMATIC FEVER			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Infections and infestations			
FOLLICULITIS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
FURUNCLE			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
INFLUENZA			
subjects affected / exposed	2 / 6 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
NASOPHARYNGITIS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
ORAL HERPES			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
HYPOKALAEMIA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
TYPE 2 DIABETES MELLITUS			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2006	Amendment 1: The rationale of this amendment is to introduce a dose reduction for Zometa for patients with renal impairment clarify the location for assessment of the bone mineral density for the primary study objectives complete possible methods for detection of metastases as secondary study objections correct a typo in the unit for the estradiol levels defining premenopausal patients expand the eligibility for the study for Node negative and Node positive patients clarify the randomization procedures at the study site and at the pharmacist site adapt the definition of an Adverse events to recent internal modifications
11 December 2006	Amendment 2: The rationale of this amendment is to allow neoadjuvant chemotherapy clarify possible nodal status for inclusion clarify definition of hormone receptor status clarify definition of premenopausal status exclude patients with other previous or concomitant malignancy specify safety reports on ONJ correct a typo in the unit for the estradiol levels defining premenopausal patients introduce some formal changes to clarify and simplify the protocol
23 November 2007	Amendment 3: The rationale of this amendment is to exclude the assessment of bone mineral density (BMD) by DXA at os calcis: The reason for this decision is that according to latest news, this measurement does not provide any additional information to measurement by QUS at os calcis. modify tumor assessment according to the German standard of care: According to German standard of care, tumor assessment by X-ray, MRI, bone scan or CT during follow-up of treatment should be performed only if clinically indicated. Therefore, tumor assessment at 24 and 60 months will be performed only if clinically indicated.
28 November 2008	Amendment 4: Only 10 out of 70 patients have been recruited since 2005. It is very unlikely that the required number of patients can be achieved in a considerable amount of time. Therefore, the enrollment of patients into this study will be stopped. The analysis of the data will be performed after LPLV. The analysis of the data of the included patients will be conducted by simple descriptive statistics and patient data listings.

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.

Study was terminated due to slow recruitment. Sample size could not be achieved and the study was terminated after enrolling only 11 patients.

Notes: