Clinical trial results:
Neoadjuvant therapy for postmenopausal women with ER and/or PgR positive breast cancer. A randomized open phase II trial evaluating the efficacy of a 6 months preoperative treatment with Letrozole (2.5 mg/day) with or without Zoledronic acid (4 mg every 4 weeks) - FEMZONE -

Summary

EudraCT number	2004-004007-37
Trial protocol	DE
Global end of trial date	03 February 2016

Results information

Result version number	v2 (current)
This version publication date	20 May 2017
First version publication date	03 March 2017
Version creation reason	
Summary attachment (see zip file)	CZOL446GDE19 (CZOL446GDE19.pdf)

Trial information

Trial identification

Sponsor protocol code	CZOL446GDE19

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 61-324-1111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 61-324-1111,

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	03 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 February 2016
Global end of trial reached?	Yes
Global end of trial date	03 February 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To show that the combination of letrozole (2.5 mg/day) and zoledronic acid (4 mg q4w, or dose-adjusted based on renal function) is superior to letrozole (2.5 mg/day) monotherapy with respect to tumor response after 6 months pre-operative treatment in postmenopausal patients with primary breast cancer. Tumor response was defined as complete response (CR) or partial response (PR) based on MRI- or mammography and/or sonography according to modified RECIST criteria.

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	31 May 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: 168
Worldwide total number of subjects	168
EEA total number of subjects	168

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)	39
From 65 to 84 years	115

85 years and over	14

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 178 patients were screened for study eligibility at 27 study sites . Of these, 168 patients were randomized at 27 active centers and received treatment with either letrozole monotherapy (LET; N=79) or combination therapy with letrozole plus zoledronic acid (LET+ZOL; N=89).

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	Investigator, Monitor, Subject, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Letrozole (LET)

Arm description:

Letrozole 2.5 mg/day oral letrozole for approximately 6.5 months neoadjuvent treatment.

Arm type	Experimental
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

2.5 mg/day

Arm title	Letrozole +Zoledronic Acid (LET+ZOL)

Arm description:

2.5 mg/day oral letrozole for approximately 6.5 months neoadjuvant treatment plus zoledronic acid 4 mg i.v. q4w

Arm type	Experimental
Investigational medicinal product name	Zoledronic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

4 mg i.v. q4w

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

Dosage and administration details:

2.5 mg /day

Number of subjects in period 1	Letrozole (LET)	Letrozole +Zoledronic Acid (LET+ZOL)
Started	79	89
Completed	67	74
Not completed	12	15
Consent withdrawn by subject	6	1
Adverse event, non-fatal	1	6
Abnormal Laboratory Value(s)	1	1
Administrative Problems	-	1
Lack of efficacy	4	4
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Letrozole (LET)
Reporting group description:	
Letrozole 2.5 mg/day oral letrozole for approximately 6.5 months neoadjuvent treatment.	
Reporting group title	Letrozole +Zoledronic Acid (LET+ZOL)
Reporting group description:	
2.5 mg/day oral letrozole for approximately 6.5 months neoadjuvant treatment plus zoledronic acid 4 mg i.v. q4w	

Reporting group values	Letrozole (LET)	Letrozole +Zoledronic Acid (LET+ZOL)	Total
Number of subjects	79	89	168
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)	19	20	39
From 65-84 years	54	61	115
85 years and over	6	8	14
Age Continuous Units: years			
arithmetic mean	70.5	71.3	
standard deviation	± 8.4	± 9.2	-
Gender, Male/Female Units: Subjects			
Female	79	89	168
Male	0	0	0

End points

End points reporting groups

Reporting group title	Letrozole (LET)
Reporting group description:	
Letrozole 2.5 mg/day oral letrozole for approximately 6.5 months neoadjuvent treatment.	
Reporting group title	Letrozole +Zoledronic Acid (LET+ZOL)
Reporting group description:	
2.5 mg/day oral letrozole for approximately 6.5 months neoadjuvant treatment plus zoledronic acid 4 mg i.v. q4w	

Primary: Tumor response rate (complete response (CR) or partial response (PR)) based on MRI- or mammography and/or sonography according to modified RECIST criteria at month 6

End point title	Tumor response rate (complete response (CR) or partial response (PR)) based on MRI- or mammography and/or sonography according to modified RECIST criteria at month 6
End point description:	
Sum of longest diameter for all target lesions was reported as baseline sum LD. Baseline sum LD was used as reference to characterize objective tumor response. Response Evaluation Criteria in Solid Tumors has 4 response categories. CR (complete response) = disappearance of all target lesions, PR (partial response)= 30% decrease in sum of longest diameter of target lesions, PD (progressive disease) = 20% increase in the sum of the longest diameter of target lesions and SD(stable disease)=small changes that do not meet criteria. Analysis was underpowered due to insufficient recruitment rate.	
End point type	Primary
End point timeframe:	
6 months	

End point values	Letrozole (LET)	Letrozole +Zoledronic Acid (LET+ZOL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	65		
Units: percentage of participants				
number (confidence interval 95%)	54.5 (41.8 to 66.9)	69.2 (56.6 to 80.1)		

Statistical analyses

Statistical analysis title	letrozole vs. letrozole+zoledronic acid
Comparison groups	Letrozole (LET) v Letrozole +Zoledronic Acid (LET+ZOL)

Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.106
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	14.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	31.1

Secondary: Best RECIST response based on central review

End point title	Best RECIST response based on central review

End point description:

Best response is defined as the best response the patients has reached during the 6 months of treatment. Response Evaluation Criteria in Solid Tumors (RECIST) has 4 response categories. CR (complete response) = disappearance of all target lesions, PR (partial response) = 30% decrease in the sum of the longest diameter of target lesions, PD (progressive disease) = 20% increase in the sum of the longest diameter of target lesions and SD (stable disease) = small changes that do not meet criteria.

End point type	Secondary

End point timeframe:

6 Months

End point values	Letrozole (LET)	Letrozole +Zoledronic Acid (LET+ZOL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	65		
Units: Participants				
Complete Response (CR)	0	2		
at least Paratial Response (PR)	36	43		
at least Stable Disease (SD)	30	19		
Progressive Disease	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with breast conserving surgery

End point title	Number of patients with breast conserving surgery

End point description:

End point type	Secondary
End point timeframe:	
Every 6 months	

End point values	Letrozole (LET)	Letrozole +Zoledronic Acid (LET+ZOL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	81		
Units: Participants				
Surgery performed	66	77		
Radical mastectomy	10	12		
Modfied radical mastectomy	3	8		
Lumpectomy/Quadrantectomy	50	56		
Lumpectomy/Quadrantectomy + Other	1	1		
Other	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Tumor Size (longest diameter) at Month 6

End point title	Change from Baseline in Tumor Size (longest diameter) at Month 6
End point description:	
Tumor size (sum of longest diameter)was analyzed based on the diameters values provided with the central review.	
End point type	Secondary
End point timeframe:	
Baseline, Month 6	

End point values	Letrozole (LET)	Letrozole +Zoledronic Acid (LET+ZOL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	65		
Units: cm				
arithmetic mean (standard deviation)	-1.12 (± 0.92)	-1.37 (± 0.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean changes in FACT-B total score over time (ITT, data as observed)

End point title	Mean changes in FACT-B total score over time (ITT, data as observed)

End point description:

The FACT-B total score is calculated by summing all five unweighted subscale scores, with total scores in the range of 0–144.To Derive a FACT-B total score: all sections added together The higher the score the better the QoL _____ + _____ + _____ + _____ + _____ =_____=FACT-B Total score (PWB score) (SWB score) (EWB score) (FWB score) (BCS score)

End point type	Secondary

End point timeframe:

baseline and 6 mos

End point values	Letrozole (LET)	Letrozole +Zoledronic Acid (LET+ZOL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=67,68)	113.3 (± 16.6)	109.5 (± 20.2)		
Month 6 (n=64,58)	112 (± 19.6)	108.2 (± 20.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE:
AEs were collected from First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All AEs reported in this record were from date of First Subject First Treatment until LSLV.

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Letrozole

Reporting group description:

Letrozole

Reporting group title	Letrozole plus zoledronic acid

Reporting group description:

Letrozole plus zoledronic acid

Serious adverse events	Letrozole	Letrozole plus zoledronic acid	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 79 (3.80%)	14 / 89 (15.73%)	
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 ovarian tumour			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contralateral breast cancer			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial insufficiency			

subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 79 (0.00%)	3 / 89 (3.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
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			
Pulmonary embolism			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhonchi			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Blood sodium decreased			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
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			
Accident			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 79 (0.00%)	4 / 89 (4.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Seroma			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			

subjects affected / exposed	1 / 79 (1.27%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
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			
Arthralgia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 89 (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			
Appendicitis perforated			
subjects affected / exposed	1 / 79 (1.27%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 89 (1.12%)	
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	Letrozole	Letrozole plus zoledronic acid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 79 (70.89%)	67 / 89 (75.28%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	25 / 79 (31.65%)	19 / 89 (21.35%)	
occurrences (all)	26	20	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 79 (10.13%)	8 / 89 (8.99%)	
occurrences (all)	12	8	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 79 (0.00%)	5 / 89 (5.62%)	
occurrences (all)	0	5	
Fatigue			
subjects affected / exposed	13 / 79 (16.46%)	20 / 89 (22.47%)	
occurrences (all)	14	21	
Pyrexia			

subjects affected / exposed	1 / 79 (1.27%)	5 / 89 (5.62%)	
occurrences (all)	1	5	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 79 (5.06%)	4 / 89 (4.49%)	
occurrences (all)	4	4	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 79 (7.59%)	3 / 89 (3.37%)	
occurrences (all)	6	3	
Diarrhoea			
subjects affected / exposed	7 / 79 (8.86%)	10 / 89 (11.24%)	
occurrences (all)	8	10	
Dry mouth			
subjects affected / exposed	5 / 79 (6.33%)	0 / 89 (0.00%)	
occurrences (all)	5	0	
Nausea			
subjects affected / exposed	8 / 79 (10.13%)	12 / 89 (13.48%)	
occurrences (all)	8	13	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 79 (3.80%)	9 / 89 (10.11%)	
occurrences (all)	3	9	
Pruritus			
subjects affected / exposed	4 / 79 (5.06%)	3 / 89 (3.37%)	
occurrences (all)	4	4	
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 79 (3.80%)	6 / 89 (6.74%)	
occurrences (all)	3	6	
Insomnia			
subjects affected / exposed	3 / 79 (3.80%)	6 / 89 (6.74%)	
occurrences (all)	3	6	
Sleep disorder			
subjects affected / exposed	5 / 79 (6.33%)	1 / 89 (1.12%)	
occurrences (all)	5	1	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	16 / 79 (20.25%)	18 / 89 (20.22%)	
occurrences (all)	17	22	
Back pain			
subjects affected / exposed	3 / 79 (3.80%)	5 / 89 (5.62%)	
occurrences (all)	3	5	
Bone pain			
subjects affected / exposed	7 / 79 (8.86%)	19 / 89 (21.35%)	
occurrences (all)	7	19	
Muscle spasms			
subjects affected / exposed	0 / 79 (0.00%)	5 / 89 (5.62%)	
occurrences (all)	0	5	
Myalgia			
subjects affected / exposed	5 / 79 (6.33%)	4 / 89 (4.49%)	
occurrences (all)	5	5	
Pain in extremity			
subjects affected / exposed	2 / 79 (2.53%)	5 / 89 (5.62%)	
occurrences (all)	2	5	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 79 (8.86%)	4 / 89 (4.49%)	
occurrences (all)	7	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 79 (3.80%)	5 / 89 (5.62%)	
occurrences (all)	3	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2007	Adjustment of the time frame between tumor assessment and randomization to clinical routine: A time window of 4 weeks of the tumor assessment until randomization was now permitted instead of 3 weeks. Alternative method for tumor assessment: MRI mammography was additionally allowed. The chosen method at Baseline however, was to be used throughout the entire study period. Change in the number of blood samples taken for the pharmacogenetics substudy: For the analyses of gene expression and polymorphisms one blood sample was considered sufficient. This blood sample should preferably be collected at the baseline visit, but could be taken at any time during the course of the study. Adjustment of timelines to the current enrollment rate.
29 October 2007	Amendment 2 (release date 29-OCT-2007) was introduced to give patients enrolled in this study the opportunity to additionally participate in the SENTINA-substudy (a multicenter study across various main studies to evaluate sentinel node biopsy within the context of neoadjuvant therapy concepts in breast cancer). Eventually, no FEMZONE patients were enrolled in the SENTINA substudy.
08 January 2010	Update of the adverse effects of letrozole and zoledronic acid as well as some other minor administrative updates in the patient information and IC form. Announcement of the premature stop of study enrollment in June 2010 due to the slow enrollment rate with the expectation to have at least 200 patients enrolled at that time. Adjustment of the time frame between tumor assessment and randomization to clinical routine: A time window of 6 weeks of the tumor assessment until randomization was now permitted instead of 4 weeks as per Amendment 1 (and 3 weeks according to the original study protocol). Adjustment of timelines to the current enrolment rate.

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 terminated after 178 patients screened and 168 randomized, due to insufficient recruitment rate (no safety issues decided the reason to terminate study). LPLV for study was on 13-DEC-2010. LPLV of the 5-year follow-up period was on 03-FEB-2016.

Notes: