Clinical trial results:
Effectiveness of Zometa treatment for the prevention of bone metastases in high risk prostate cancer patients. A randomized, open-label, multicenter study of the European Association of Urology (EAU) in Cooperation with the Scandinavian Prostate Cancer Group (SPCG) and the Arbeitsgemeinschaft Urologische Onkologie (AUO)

Summary

EudraCT number	2004-001786-18
Trial protocol	IT
Global end of trial date	17 January 2014

Results information

Result version number	v1 (current)
This version publication date	04 June 2016
First version publication date	04 June 2016
Summary attachment (see zip file)	Zeus clinical study report synopsis (Zeus clinical study report Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	CZOL446GDE08

Additional study identifiers

ISRCTN number	ISRCTN66626762
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	European Association of Urology
Sponsor organisation address	Mr. E.N. van Kleffensstraat 5, Arnhem, Netherlands,
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Scientific contact	Clinical Research Associate, Dario Draga`, 39 335 5611720, dario.draga@iperbole.bologna.it
Sponsor organisation name	European Association of Urology
Sponsor organisation address	Mr. E.N. van Kleffensstraat 5, Arnhem, Netherlands, 6842 CV
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	17 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 January 2014
Global end of trial reached?	Yes
Global end of trial date	17 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to show superiority of zoledronic acid as compared to control in the proportion of patients with at least one bone metastasis after 48 months of treatment.

Protection of trial subjects:

Serum creatinine is to be measured prior to each dose of study drug.
Patients are advised, if possible, to avoid invasive dental procedures during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 June 2004
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	Spain: 70
Country: Number of subjects enrolled	Italy: 123
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Switzerland: 15
Country: Number of subjects enrolled	Germany: 741
Country: Number of subjects enrolled	Denmark: 66
Country: Number of subjects enrolled	Finland: 86
Country: Number of subjects enrolled	France: 79
Country: Number of subjects enrolled	Greece: 24
Country: Number of subjects enrolled	Netherlands: 121
Country: Number of subjects enrolled	Norway: 45
Country: Number of subjects enrolled	Sweden: 27
Country: Number of subjects enrolled	Turkey: 27
Worldwide total number of subjects	1433
EEA total number of subjects	1391

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)	507
From 65 to 84 years	913
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

From June 2004 to August 2007, 1433 patients were randomized in 13 participating countries (Belgium, Switzerland, Germany, Denmark, Spain, Finland, France, Greece, Italy, The Netherlands, Norway, Sweden and Turkye).

Pre-assignment

Screening details:

Patients were screened to check whether they met the in- and exclusioncriteria.

Period 1

Period 1 title	randomization period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Zometa group

Arm description:

Zometa administered intravenously as a 15-minute infusion every 3 months for a treatment period of 48 months

Arm type	Active comparator
Investigational medicinal product name	zoledronic acid
Investigational medicinal product code	
Other name	Zometa
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Zoledronic acid was administered intravenously as a 15-minute infusion every 3 months for a treatment period of 48 months.
Patients were treated with Zometa 4 mg if at baseline the creatinine clearance was > 60 mL/min.
For patients with mild to moderate renal impairment (30 mL/min < creatinine clearance ≤ 60 mL/min) at baseline the dose of Zometa was adjusted.
Zoledronic acid was provided in plastic vials containing 4 mg zoledronic acid in 5 mL concentrate solution for infusion. Each zoledronic acid plastic vial contained 4 mg zoledronic acid (anhydrous). The zoledronic acid 4 mg/5 mL concentrate solution was not for direct infusion and was further diluted prior to the use.

Arm title	Control group

Arm description:

No investigational treatment

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Zometa group	Control group
Started	716	717
Completed	694	699
Not completed	22	18
Consent withdrawn by subject	13	14
ineligible	5	2
Lost to follow-up	4	2

Period 2

Period 2 title	treatment period (intention to treat)
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Zometa group

Arm description:

Zometa administered intravenously as a 15-minute infusion every 3 months for a treatment period of 48 months

Arm type	Active comparator
Investigational medicinal product name	zoledronic acid
Investigational medicinal product code	
Other name	Zometa
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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Zoledronic acid was provided in plastic vials containing 4 mg zoledronic acid in 5 mL concentrate solution for infusion. Each zoledronic acid plastic vial contained 4 mg zoledronic acid (anhydrous). The zoledronic acid 4 mg/5 mL concentrate solution was not for direct infusion and was further diluted prior to the use.

Arm title	Control group

Arm description:

No investigational treatment

Arm type	No intervention

No investigational medicinal product assigned in this arm

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: treatment period (ITT population) is used, see also article.

Number of subjects in period 2[2]	Zometa group	Control group
Started	694	699
Completed	440	477
Not completed	254	222
Adverse event, serious fatal	23	47
Consent withdrawn by subject	47	38
Physician decision	17	18
Adverse event, non-fatal	57	10
administrative problems	12	12
Lost to follow-up	21	26
Lack of efficacy	70	58
Protocol deviation	7	13

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: treatment period (ITT population) is used, see also article.

Baseline characteristics

Reporting groups	
Reporting group title	Zometa group
Reporting group description:	
Zometa administered intravenously as a 15-minute infusion every 3 months for a treatment period of 48 months	
Reporting group title	Control group
Reporting group description:	
No investigational treatment	

Reporting group values	Zometa group	Control group	Total
Number of subjects	694	699	1393
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	67	67	
standard deviation	± 8	± 8	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	694	699	1393
Prior local curative treatment			
Units: Subjects			
prostatectomy	322	311	633
radiotherapy	51	49	100
prostatectomy and radiotherapy	18	19	37
no prior local curative treatment	303	320	623
PSA category at diagnosis			
Units: Subjects			
PSA < 20 ng/ml	305	321	626
PSA > = 20 ng/ml	389	378	767
Gleason score at diagnosis			
Units: Subjects			
Gleason < 8	267	259	526
Gleason >= 8	427	440	867
Nodal status at baseline			
Units: Subjects			

N0	302	333	635
N1	181	152	333
Nx	211	214	425
ADT			
Androgen Deprivation Therapy (ADT) continued or started at randomization or started within 6 weeks after randomization			
Units: Subjects			
ADT yes	430	442	872
ADT no	264	257	521
race Units: Subjects			
caucasian	650	659	1309
black	2	0	2
oriental	3	2	5
other	39	38	77
PSA value at diagnosis Units: ng/ml			
arithmetic mean	39.8	40.2	
standard deviation	± 70	± 75.8	-
Time from diagnosis to study entry Units: months			
arithmetic mean	18.7	20.2	
standard deviation	± 24	± 42	-

End points

End points reporting groups

Reporting group title	Zometa group
Reporting group description:	
Zometa administered intravenously as a 15-minute infusion every 3 months for a treatment period of 48 months	
Reporting group title	Control group
Reporting group description:	
No investigational treatment	
Reporting group title	Zometa group
Reporting group description:	
Zometa administered intravenously as a 15-minute infusion every 3 months for a treatment period of 48 months	
Reporting group title	Control group
Reporting group description:	
No investigational treatment	

Primary: Paired bone imaging central review

End point title	Paired bone imaging central review
End point description:	
Bone imaging procedures were centrally reviewed after blinding. The possible outcomes of the central review were: non metastatic, metastatic, or equivocal. From 612 patients both baseline and follow-up bone imaging procedures were available for central review. The central reviewer indicated that 12 of 612 patients had bone metastases at baseline, and these were excluded.	
End point type	Primary
End point timeframe:	
At 4 ± 0.5 years	

End point values	Zometa group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280[1]	320[2]		
Units: subjects				
metastatic	36	34		
equivocal	37	23		
non-metastatic	207	263		

Notes:

[1] - central review paired analysis

[2] - central review paired analysis

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Zometa group v Control group

Number of subjects included in analysis	600
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.13
Method	Chi-squared

Primary: bone imaging local result

End point title	bone imaging local result

End point description:

There were 1040 patients who had undergone a bone imaging procedure and for whom the Bone Metastases outcome status (local evaluation) at 4 ± 0.5 years was available.

End point type	Primary

End point timeframe:

At 4 ± 0.5 years

End point values	Zometa group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	515	525		
Units: subjects				
metastatic	88	89		
non metastatic	427	436		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Zometa group v Control group
Number of subjects included in analysis	1040
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.954
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	4.7

Primary: bone imaging local result

End point title	bone imaging local result

End point description:

In some patients bone imaging procedures were performed at a later time point during the follow up period (> 4,5 years after visit 1). When also taking these patients into account, results from 534 patients in the Zometa group and 540 patients in the Control group are available.

End point type	Primary

End point timeframe:

After a median follow up of 4.8 years

End point values	Zometa group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	534	540		
Units: subjects				
metastatic	95	91		
non metastatic	439	449		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Control group v Zometa group
Number of subjects included in analysis	1074
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.684
Method	Chi-squared

Primary: patients with bone metastases

End point title	patients with bone metastases

End point description:

End point type	Primary

End point timeframe:

After a median follow up of 4.8 years

End point values	Zometa group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	694	699		
Units: patients				
bone metastases YES	95	91		
bone metastases NO	599	608		

Statistical analyses

Statistical analysis title	Kaplan Meier
Comparison groups	Zometa group v Control group
Number of subjects included in analysis	1393
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.653
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported during the 48 months treatment period.

Adverse event reporting additional description:

Information about adverse events was collected during each study visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	5

Reporting groups

Reporting group title	Zometa treated group

Reporting group description:

Zometa administered intravenously as a 15-minute infusion every 3 months for a treatment period of 48 months.
All patients who received at least one dose of Zometa .Some patients (n=8) were randomized for the control group but received Zometa and, in the safety analysis, are taken into account in the Zometa treated group.

Reporting group title	Control group

Reporting group description:

No investigational treatment
All patients who underwent at least visit 2.
Some patients (n=8) were randomized for the control group but received Zometa and, in the safety analysis, are taken into account in the Zometa treated group.
One patient in the Control group who was ineligible but for whom safety information was available, was taken into account in the safety analysis, but not in the efficacy analysis.

Serious adverse events	Zometa treated group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	233 / 702 (33.19%)	264 / 692 (38.15%)	
number of deaths (all causes)	127	138	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified			
subjects affected / exposed	38 / 702 (5.41%)	32 / 692 (4.62%)	
occurrences causally related to treatment / all	1 / 47	0 / 45	
deaths causally related to treatment / all	0 / 13	0 / 14	
Vascular disorders			
vascular disorders			
subjects affected / exposed	8 / 702 (1.14%)	12 / 692 (1.73%)	
occurrences causally related to treatment / all	0 / 11	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 4	

Surgical and medical procedures			
surgical and medical procedures			
subjects affected / exposed	6 / 702 (0.85%)	9 / 692 (1.30%)	
occurrences causally related to treatment / all	0 / 6	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
general disorderd and administration site conditions			
subjects affected / exposed	14 / 702 (1.99%)	13 / 692 (1.88%)	
occurrences causally related to treatment / all	5 / 18	0 / 13	
deaths causally related to treatment / all	0 / 5	0 / 10	
Immune system disorders			
immune system disorder			
subjects affected / exposed	1 / 702 (0.14%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
social circumstances			
subjects affected / exposed	0 / 702 (0.00%)	1 / 692 (0.14%)	
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			
reproductive system and breast disorders			
subjects affected / exposed	2 / 702 (0.28%)	3 / 692 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	6 / 702 (0.85%)	8 / 692 (1.16%)	
occurrences causally related to treatment / all	0 / 11	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 2	
Psychiatric disorders			
psychiatric disorders			

subjects affected / exposed	2 / 702 (0.28%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
hepatobiliary disorders			
subjects affected / exposed	1 / 702 (0.14%)	7 / 692 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
investigations			
subjects affected / exposed	0 / 702 (0.00%)	1 / 692 (0.14%)	
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			
inury, poisoning and procedural complications			
subjects affected / exposed	17 / 702 (2.42%)	20 / 692 (2.89%)	
occurrences causally related to treatment / all	0 / 22	0 / 25	
deaths causally related to treatment / all	0 / 0	0 / 1	
Congenital, familial and genetic disorders			
congenital, familial and genetic disorders			
subjects affected / exposed	0 / 702 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
cardiac disorders			
subjects affected / exposed	29 / 702 (4.13%)	37 / 692 (5.35%)	
occurrences causally related to treatment / all	2 / 36	0 / 50	
deaths causally related to treatment / all	0 / 8	0 / 10	
Nervous system disorders			
nervous system disorder			
subjects affected / exposed	16 / 702 (2.28%)	15 / 692 (2.17%)	
occurrences causally related to treatment / all	1 / 21	0 / 25	
deaths causally related to treatment / all	0 / 2	0 / 1	
Blood and lymphatic system disorders			

Blood and lymphatic system disorders			
subjects affected / exposed	3 / 702 (0.43%)	4 / 692 (0.58%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
ear and labyrinth disorders			
subjects affected / exposed	3 / 702 (0.43%)	2 / 692 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
eye disorders			
subjects affected / exposed	2 / 702 (0.28%)	3 / 692 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
gastrointestinal disorders			
subjects affected / exposed	13 / 702 (1.85%)	16 / 692 (2.31%)	
occurrences causally related to treatment / all	2 / 21	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
skin and subcutaneous tissue disorders			
subjects affected / exposed	1 / 702 (0.14%)	2 / 692 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
renal and urinary disorders			
subjects affected / exposed	19 / 702 (2.71%)	31 / 692 (4.48%)	
occurrences causally related to treatment / all	1 / 34	0 / 36	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endocrine disorders			
endocrine disorders			
subjects affected / exposed	1 / 702 (0.14%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	22 / 702 (3.13%)	17 / 692 (2.46%)	
occurrences causally related to treatment / all	9 / 27	0 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
infections and infestations			
subjects affected / exposed	29 / 702 (4.13%)	28 / 692 (4.05%)	
occurrences causally related to treatment / all	0 / 34	0 / 37	
deaths causally related to treatment / all	0 / 1	0 / 3	
Metabolism and nutrition disorders			
metabolism and nutrition disorders			
subjects affected / exposed	3 / 702 (0.43%)	2 / 692 (0.29%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Zometa treated group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	554 / 702 (78.92%)	512 / 692 (73.99%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	61 / 702 (8.69%)	90 / 692 (13.01%)	
occurrences (all)	62	95	
Hypertension			
subjects affected / exposed	59 / 702 (8.40%)	37 / 692 (5.35%)	
occurrences (all)	61	38	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	54 / 702 (7.69%)	3 / 692 (0.43%)	
occurrences (all)	91	4	
Fatigue			
subjects affected / exposed	29 / 702 (4.13%)	36 / 692 (5.20%)	
occurrences (all)	39	42	

Pyrexia			
subjects affected / exposed	70 / 702 (9.97%)	9 / 692 (1.30%)	
occurrences (all)	115	9	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	35 / 702 (4.99%)	34 / 692 (4.91%)	
occurrences (all)	38	38	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	72 / 702 (10.26%)	45 / 692 (6.50%)	
occurrences (all)	98	57	
Back pain			
subjects affected / exposed	59 / 702 (8.40%)	38 / 692 (5.49%)	
occurrences (all)	65	42	
Myalgia			
subjects affected / exposed	36 / 702 (5.13%)	9 / 692 (1.30%)	
occurrences (all)	58	10	
Infections and infestations			
Influenza			
subjects affected / exposed	42 / 702 (5.98%)	18 / 692 (2.60%)	
occurrences (all)	64	21	
Nasopharyngitis			
subjects affected / exposed	41 / 702 (5.84%)	42 / 692 (6.07%)	
occurrences (all)	60	56	
Urinary tract infection			
subjects affected / exposed	45 / 702 (6.41%)	35 / 692 (5.06%)	
occurrences (all)	67	48	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2003	Change in inclusion criterium; instead of only hormone naive patients, also patients receiving androgen deprivation therapy were allowed. The definition of abnormal renal function was changed. Change in bone turnover parameters.
10 February 2004	Originally, for the sample size calculation, an event rate in high risk prostate cancer patients not treated with Zometa of 25%, which was based on expert opinion, was assumed. However, with the adoption of new inclusion criteria a reduced proportion of events was expected and concerns were raised regarding the fact that the sample size calculation in the current study was based on a very large treatment effect of Zometa on time to symptomatic bone metastases and there was certainly a risk of the study being underpowered. Introduction of review of the safety data at 12 months from study starting, by an Independent Data Monitoring Committee.
08 June 2005	During the Steering Committee that took place in Munich on March 31st 2004 it was decided to re-introduce the sub-study on bone mineral density, that was erroneously cancelled with the Amendment 1. Therefore, Amendment 4 re-introduced all the parts that were deleted with Amendment 1 as far as the sub-study on bone mineral density was concerned. Since in the original protocol no limitation of the time-window between two infusions of the experimental drug was reported, it was decided that the maximum time for Zometa discontinuation should be 16 weeks. Administration of the drug beyond 16 weeks after the last Zometa infusion would be considered as a major protocol deviation. Due to changes made, at that time, to Zometa prescribing information, an amendment to clinical study protocols with Zometa was required. These changes involved two areas: - Dose reduction for patients with renal impairment: - Osteonecrosis of the jaw (ONJ): The instructions for rapid notification of serious adverse events were revised according to local internal procedure of Novartis subsidiaries of the countries involved in the trial. It was specified that the FDA form 1572 was not needed as one of the essential documents of the study. Therefore, the document was not collected anymore. Staging of Prostate Cancer in protocol Appendix 3 was replaced by the latest TNM Classification (American Joint Committee on Cancer, 2002).

17 October 2006	1) to introduce an expedited report in case of occurrence of osteonecrosis of the jaw (ONJ) and in cases of osteomyelitis. While ONJ was reported in cancer patients receiving bisphosphonates as a component of their therapy, the etiology and pathogenesis of ONJ are not clear. In order to better understand and assess ONJ, all cases of ONJ and osteomyelitis were to be expedited as 15-day reports. 2) Planning of an interim analysis In the presence of strong evidence of treatment effect with Zometa in preventing bone metastases, the total study duration would be shortened.
27 November 2009	1) The change of the study statistician. 2) The change of Steering Committee (SC) membership. 3) The inclusion of a mandatory bone scan in ALL patients still on-study and a second interim analysis, as a consequence of the first interim analysis results. 4) The inclusion of a blind central imaging review.
08 December 2011	During the Steering Committee and National Coordinators Meeting in March 2011, interim results relating to the development of bone metastases were evaluated. Analyses in December 2010 showed that 9% of patients developed bone metastases. At the end of the study (December 2011), when, at that time, looking at the status of patients who developed metastases, it was clear that it was unlikely that the 18% event rate as assumed in the protocol would be reached. With a prolonged follow up of another 2 years, it was very likely that we would have sufficient events for a powerful analysis. Therefore a 2 years longer follow up then anticipated originally in the protocol was proposed. During this period follow up information on the development of bone metastases and survival was collected yearly for each patient that was, at that time, followed for progression or survival in the ZEUS study. Only information on progression and survival was collected.

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/24630685