



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, |
| Public contact | Clinical Research Associate, Dario Draga`, 39 335 5611720, dario.draga@iperbole.bologna.it |
| 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 |
| Public contact | C.T.M. Caris, European Association of Urology, c.caris@uroweb.org |
| Scientific contact | Dr. W.P.J. Witjes, European Association of Urology, w.witjes@uroweb.org |

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 Turkey).

Pre-assignment

Screening details:

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

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:

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

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 occurrences causally related to treatment / all deaths causally related to treatment / all | 6 / 702 (0.85%) 0 / 6 0 / 0 | 9 / 692 (1.30%) 0 / 11 0 / 0 | |
| General disorders and administration site conditions general disorderd and administration site conditions subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 14 / 702 (1.99%) 5 / 18 0 / 5 | 13 / 692 (1.88%) 0 / 13 0 / 10 | |
| Immune system disorders immune system disorder subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 702 (0.14%) 0 / 1 0 / 0 | 1 / 692 (0.14%) 0 / 1 0 / 0 | |
| Social circumstances social circumstances subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 702 (0.00%) 0 / 0 0 / 0 | 1 / 692 (0.14%) 0 / 1 0 / 0 | |
| Reproductive system and breast disorders reproductive system and breast disorders subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 702 (0.28%) 0 / 3 0 / 0 | 3 / 692 (0.43%) 0 / 5 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 6 / 702 (0.85%) 0 / 11 0 / 0 | 8 / 692 (1.16%) 0 / 14 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 | | | |
| injury, 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 occurrences (all) | 70 / 702 (9.97%) 115 | 9 / 692 (1.30%) 9 | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 35 / 702 (4.99%) 38 | 34 / 692 (4.91%) 38 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) | 72 / 702 (10.26%) 98 59 / 702 (8.40%) 65 36 / 702 (5.13%) 58 | 45 / 692 (6.50%) 57 38 / 692 (5.49%) 42 9 / 692 (1.30%) 10 | |
| Infections and infestations Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) | 42 / 702 (5.98%) 64 41 / 702 (5.84%) 60 45 / 702 (6.41%) 67 | 18 / 692 (2.60%) 21 42 / 692 (6.07%) 56 35 / 692 (5.06%) 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 | <p>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.</p> <p>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.</p> <p>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:</p> <ul style="list-style-type: none">- Dose reduction for patients with renal impairment:- Osteonecrosis of the jaw (ONJ): <p>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.</p> <p>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).</p> |

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|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 17 October 2006 | <p>1) to introduce an expedited report in case of occurrence of osteonecrosis of the jaw (ONJ) and in cases of osteomyelitis.</p> <p>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.</p> <p>2) Planning of an interim analysis</p> <p>In the presence of strong evidence of treatment effect with Zometa in preventing bone metastases, the total study duration would be shortened.</p> |
| 27 November 2009 | <p>1) The change of the study statistician.</p> <p>2) The change of Steering Committee (SC) membership.</p> <p>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.</p> <p>4) The inclusion of a blind central imaging review.</p> |
| 08 December 2011 | <p>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.</p> <p>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.</p> <p>Therefore a 2 years longer follow up then anticipated originally in the protocol was proposed.</p> <p>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.</p> |

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>