Synopsis

Study Title and number	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). Protocol No. CZOL446G DE08 SPCG Protocol No. 11 Zometa® (Zoledronic Acid, CGP42446)
EudraCT nr	2004-001786-18
Publication	http://dx.doi.org/10.1016/j.eururo.2014.02.014
Study period	Date of first enrolment: 08 June 2004 Date of last completed: 17 January 2014
Objectives	**Primary objective**: 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. **Secondary study objectives:** • to evaluate the effect of zoledronic acid on the time to the first bone metastasis irrespective whether symptomatic or not • to evaluate the effect of zoledronic acid on overall survival. • to evaluate the effect of zoledronic acid on serum PSA doubling time • to evaluate the effect of zoledronic acid on biochemical markers of bone turnover (selected centers only) • to evaluate the effect of zoledronic acid on bone mineral density at two and four years after randomization in patients receiving hormonal therapy at study entry (substudy in selected centers)
Methodology	Prospective, multi-centre, randomized, open-label, two-arm study in parallel groups
Number of patients	1433 patients were randomized, 716 patients Zometa treated and 717 control patients. 1393 patients (694 Zometa treated and 699 control patients) were included in the ITT analysis.
Diagnosis and main inclusion criteria	Male patients aged 18+, with non-metastatic prostate cancer with at least one of the following conditions: - Gleason Score 8-10 - pN+ - PSA ≥ 20 at diagnosis Patients receiving androgen deprivation by orchiectomy or administration of GnRH analogue ± anti-androgens or no androgen deprivation.
Study treatment	All patients meeting the study entry criteria were randomly assigned in a ratio of 1:1 to receive either: • Zometa® administered intravenously as a 15-minute infusion every 3 months for a treatment period of 48 months and a supplement of calcium 500 mg and 400-500 I.U. vitamin D or • a supplement of calcium 500 mg and 400-500 I.U. vitamin D alone

Criteria for evaluation	**Primary efficacy variable:** • Number of patients who developed at least one bone metastasis after 48 months of treatment **Secondary efficacy variables:** • Time to first bone metastasis • Overall survival • Serum PSA doubling time • Parameters of bone turnover • Bone mineral density **Safety:** • Serum creatinine • (Serious) Adverse events
Statistical methods	This was a clinical study to show superiority of Zometa in the proportion of patients with at least one bone metastasis in high risk prostate cancer patients as compared to a control group. Data of all centers was pooled to reach an adequate sample size. Data were summarized with respect to demographic and baseline characteristics, efficacy observations and measurements as well as safety observations and measurements. If it was deemed to be useful, summaries were done in addition for each stratum separately. Number of valid observations and summary statistics (mean, standard deviation, median, maximum, minimum) were presented for continuous variables. Absolute and relative frequencies were tabulated for categorical data. In addition to the p-value for the testing procedure the corresponding confidence intervals have been computed. The comparison was done on the two-sided 5%-level.
Summary conclusions	**Efficacy** No difference was shown in the occurrence of bone metastases between treatment groups. The central review results led to similar conclusions. When specifically focussing on the subgroup receiving Androgen deprivation therapy, no differences could be detected. **Safety** The observed adverse events are in line with the known site effects of Zometa. No SUSAR's have been reported in this trial. **Conclusion** Zoledronic acid administered every 3 months was demonstrated to be ineffective to prevent bone metastases at 4 years