Sponsor

Novartis Pharma GmbH

Generic Drug Name

Zoledronic acid

Therapeutic Area of Trial

Patients with prostate cancer or breast cancer and bone metastasis

Approved Indication

- Indicated for prevention of skeletal-related complications of patients with advanced cancer disease extended to the skeleton
- Indicated for the treatment of tumor-induced hypercalcemia (TIH)

Study Number

CZOL446EDE28

Title

Effect of intravenous Zoledronic Acid on Bone Metabolism given over 4 months in patients with prostate cancer or breast cancer and bone metastasis. A prospective, single-arm multicenter study.

Phase of Development

Phase IV

Study Start/End Dates

10 May 2006 to 14 July 2009

Study Design/Methodology

The study was a prospective, single group, open label, multi center study on serum bone turnover markers in patients with prostate or breast cancer with bone metastasis treated with zoledronic acid (dosage according to calculated creatinine clearance, see 3.4.1) which was to be administered i.v. every 4 weeks for a 4 months treatment period (Day 1, 9, 57 and 85).

Centres

98 centers in Germany

Principle Investigator: J. Gschwend

Objectives

Primary objective(s)

To assess course of bone turn-over markers (PINP, CTX, BSP, OPG, RANKL)

Secondary objective(s)

Relationship between tumour burden/metastatic sites assessed by bone scan (Soloway Score and level of bone markers at study entry; pain assessment (VAS) and analgesics score; relationship between pain and course of bone turn-over markers; rate of skeletal related events (SRE); relationship between SREs and bone turnover markers; quality of life (EORTC C-30 and BR-23 modules); course of PSA (patients with prostate cancer only); course of urinary NTX (in centers where storage at -20°C is possible); safety and tolerability.

Test Product (s), Dose(s), and Mode(s) of Administration

Zoledronic acid (dosage according to calculated creatinine clearance before first administration of study drug) administered as a 15-minute infusion every 4 weeks for 4 months. Study infusion visits were recommended to be within +/- 7 days of the scheduled visit. If an interval between two consecutive visits deviates from the schedule, the next visit was recommended to be performed after a 4-week interval.

Reference Product(s), Dose(s), and Mode(s) of Administration

N/A

Criteria for Evaluation

Primary variables

The parameters of interest were serum parameters of bone turn-over PINP, CTX, BSP, OPG and RANKL. The primary variables were the course of, and changes from baseline in values of these parameters as determined in the central laboratory

Secondary variables

Secondary variables were the relationship between specific concomitant therapies and level of bone markers; the relationship between tumour burden/metastatic sites and level of bone markers at study entry; the course in, and change from baseline in pain assessment (VAS score) and analgesics score; the relationship between pain and course of bone turn-over markers; the course of, and changes from baseline in prostate specific antigen (PSA, patients with prostate cancer only); the relationship between pain and course of bone turn-over markers; the incidence of skeletal related events (SRE) as well as the time to the first SRE; the relationship between SRE and bone turnover markers; health-related quality of life as measured by EORTC C-30 and BR-23 funtional scales and items; and overall survival.

Safety and tolerability

The assessment of safety was based mainly on the frequency and type of adverse events, and laboratory values (including serum creatinine).

Pharmacology

N/A

Other

N/A

Statistical Methods

Primary efficacy: The parameters of interest were serum parameters of bone turn-over PINP, CTX, BSP, OPG and RANKL. The primary variables are the values of these parameters as determined in the central laboratory. Values below the lower limit of quantification as well as values beyond the upper limit of quantification were replaced by the lower and upper limit of quantification, respectively, before analysis. Values of 0 indicated a measurement not done and were replaced by a missing value before analysis. The lower and upper limits of quantification are given in the statistical analysis plan (RAP Module 3 – Detailed statistical methodology). If not otherwise indicated, data from the follow-up visit (Day 365) were included in the display together with the data of the core phase (up to Visit 6/Day 120).

Since this clinical trial was not designed to address specific bone marker related hypotheses, the analyses of these data were exploratory and should be interpreted as hypotheses generating rather than hypothesis confirming. Additional data from subsequent clinical trials will be required to confirm any findings. Summary statistics were provided for the ITT and per-protocol sets for each parameter of bone turn-over by visit and tumor type. Summary statistics for absolute and relative changes from baseline were computed by visit and tumor type. Since it was very likely that the distribution of the data was right skewed, data were transformed using a transformation of the Box-Cox family (transformed value = ln(original value +1)). A value of one was added to minimize the influence of extremely low values. Summary statistics were computed for transformed values in the same manner as for values on the original scale. The course of the mean (plus standard deviation) was additionally displayed graphically by study day, and tumor type.

Patients who dropped out before the scheduled end of the observation period at Day 120 were included in the ITT set. Since there exists no accepted method to deal with missing values in bone markers in the presence of inherent biological variability, measurement errors, or other factors possibly influencing, the last observation carried forward (LOCF) approach described in the final study protocol was discouraged, and missing values of the primary variables were not replaced. Only observed cases were analyzed. This applied also for per-protocol analyses and secondary efficacy endpoints.

Secondary efficacy: Secondary variables were the relationship between specific concomitant therapies and level of bone markers; the relationship between tumor burden/metastatic sites and level of bone markers at study entry; the course in, and change from baseline in pain assessment (VAS score) and analgesics score; the relationship between pain and course of bone turn-over markers; the course of, and changes from baseline in prostate specific antigen (PSA, patients with prostate cancer only); the relationship between pain and course of bone turn-over markers; the incidence of skeletal related events (SRE) as well as the time to the first SRE; the relationship between SRE and bone turnover markers; health-related quality of life as measured by EORTC C-30 and BR-23 funtional scales and items; and overall survival.

Secondary efficacy variables were analyzed for the ITT set using summary statistics (including the number of observations, number of missing values, mean, standard deviation, median, minimum and maximum values) for continuous variables, and frequency tables categorical variables. Time-to-event variables (time to first SRE; overall survival) were analyzed using the Kaplan-Meier method. Where appropriate, two-sided 95% confidence intervals (95% CIs) for means and/or proportions as well as descriptive p values were provided. Confidence intervals for proportions were calculated according to the method of Clopper and Pearson.

Safety: The assessment of safety was based mainly on the frequency and type of adverse events, and laboratory values (including serum creatinine). The assessment of safety was based on the safety set.

Adverse events were summarized by presenting the number and percentage of patients having any adverse event, having any event by MedDRA system organ class and having each individual adverse event by MedDRA preferred term. Any AE with suspected drug relation, or leading to dose adjustment or temporarily interruption, or leading to perma-

nent discontinuation, or requiring concomitant medication/non-drug therapy were reported separately. The number of patients with significant AE was displayed. Any other information, e.g. start and end date, severity of adverse events or relationship to study medication was listed appropriately.

Summary statistics for laboratory values were presented by visit and as changes from baseline for hematology and biochemistry laboratory results. For serum creatinine, additionally absolute and relative frequencies of the number of increases/number of patients with any increase in serum creatinine from the value at baseline were presented.

No interim analysis was planned in the protocol nor performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Patient population:
The patient population consisted of 301 prostate cancer patients and 99 breast cancer patients. All treated patients (n=400) were analyzed with the safety set, 397 (99.3%) with the ITT set and 276 (69.0%) with the per-protocol set.

Inclusion criteria:

- Histologically proven carcinoma of the prostate with evidence of at least one cancer related bone lesion with or without hormonal treatment.
- Histologically proven carcinoma of the breast with evidence of at least one cancer related bone lesion
- Negative pregnancy test at screening in case of child-bearing potential
- Performance status ECOG 0-2
- Laboratory requirements: a) hepatic function: total bilirubin ≤ 2,5 times the upper-normal limit of the institution, SGPT, SGOT ≤ 2,5 times the upper-normal limit of the institution.
- Renal function: creatinine clearance ≥ 30 ml/min
- Normal cardiac function
- Life expectancy ≥ 6 months
- Signed informed consent prior to trial entry
- Patients of ≥ 18 years
- Patients must be accessible for treatment
- Standardized therapy for pre- und postmenopausal women is allowed
- Prior surgery, chemotherapy and radiotherapy is allowed. At least 4 weeks must have elapsed since the completion of surgery, chemotherapy and radiotherapy to breast or bone.

Exclusion criteria:

- Prior treatment with bisphosphonates within 6 months before study start, and during treatment with zoledronic acid
- No presence of at least one cancer-related bone lesion that is detectable on conventional radiographs of bone or detectable on a bone scan and confirmed by

MRT or CT at screening

- Abnormal renal function as evidenced by
- A calculated creatinine clearance < 30 ml/minute. Creatinine clearance (CrCl) is calculated using the Cockcroft-Gault formula:

  CrCl= [140-age (years)] x weight (kg) {x 0.85 for female patients}
  [72 x serum creatinine (mg/dL)]
- Patients with clinically symptomatic brain metastases
- History of diseases with influence on bone metabolism such as Paget´s disease and primary hyperparathyroidism and with need of treatment for osteoporosis (defined according to DVO, T-Score ≤2.5).
- Severe physical or psychological concomitant diseases that expected to impair compliance with the provisions of the study protocol or impair the assessment of drug of patient safety (clinically significant ascites, NYHA III or IV, cardiac failure, clinically relevant pathologic findings in ECG)
- Breast feeding or Pregnancy, confirmed by a positive serum hCG laboratory test (> 5 mIU/ml)
- Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they meet the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels >25 mIU/m or 6 weeks post surgical bilateral oophorectomy with or without hysterectomy or are using one or more medically acceptable methods of contraception.
- Known hypersensitivity to zoledronic acid or other bisphosphonates
- Corrected (adjusted for serum albumin) serum calcium concentration < 8.0 mg/dl (2.00 mmol/L) or 12.0mg/dl (3.00 mmol/L)
- Known history or present abuse of alcohol or drugs
- Subjects who, in the opinion of the investigator, are unlikely to cooperate fully during the study
- Previous Radiation therapy to bone (including therapeutic radioisotopes such as strontium 89) within 1 month
- Prior malignancy except basal cell or squamous cell skin cancer or any other cancer from which the patient has been disease-free for ≥ 5 yrs.
- Use of other investigational drugs at the time of enrollment, or within 30 days before enrollment
- Current active dental problems including infection of the teeth or jawbone (maxilla or mandibular); dental or fixture trauma, or a current or prior diagnosis of osteonecrosis of the jaw (ONJ), of exposed bone in the mouth, or of slow healing after dental procedures.
- Recent (within 6 weeks) or planned dental or jaw surgery (e.g.. extraction, implants)

Number of Subjects

	Novartis product
Randomised n	400
Intent-to-treat population (ITT) n (%)	397 (99.3)
Completed n (%)	335 (83.8)
Withdrawn n (%)	65 (16.3)
Withdrawn due to adverse events n (%)	11 (2.8)
Withdrawn due to lack of efficacy n (%)	2 (0.5)
Withdrawn for other reasons n (%)	52 (13.0)

Demographic and Background Characteristics

	Novartis product
N (ITT)	397
Females : males	98 : 299
Mean age, years (SD)	68.1 (9.5)
Mean weight, kg (SD)	n.a.
Race Caucasian n (%) Oriental n (%) Other n (%)	 383 (96.5) 1 (0.3%) 13 (3.3%)

Primary Objective Result(s)

Mean (± S. D.) course of PINP

At baseline: 227.1 (± 409.45) ng/ml, ranging from 5.9 to 2400.0 ng/ml **At study end**: 87.1 (± 197.49) ng/ml, ranging from 5.0 to 1919.0 ng/ml Mean change from baseline at study end (Visit 6): -118.6 (± 346.80) ng/ml Mean relative change from baseline at study end: -42.0% (± 103.22%)

Overall, the change from baseline at study end was significant in both, *t* test (test statistic: -5.94, d.f. 301, $p<0.0001$) as well as Wilcoxon's signed-rank test (test statistic: -18018.5, $p<0.0001$;

No statistically remarkable differences between breast and prostate cancer patients were observed.

Mean (± S.D.) course of CTX (ITT)

At baseline: 0.5 (± 0.53) ng/ml, ranging from 0.0 to 4.1 ng/ml

At study end: 0.2 (± 0.32) ng/ml, ranging from 0.0 to 2.5 ng/ml

Mean change from baseline at study end (Visit 6): -0.3 (± 0.39) ng/ml.

Mean relative change from baseline: -43.0% (± 120.28%)

Overall, the change from baseline at study end was significant in both, *t* test (test statistic: -12.19, d.f. 301, $p<0.0001$) as well as Wilcoxon's signed-rank test (test statistic: -19172.5, $p<0.0001$)

No statistically remarkable differences between breast and prostate cancer patients were observed.

Mean (± S.D.) course of OPG (ITT)

At baseline: 5.6 (± 2.24) pmol/l, ranging from 1.9 to 21.3 pmol/l **At**

study end: 5.6 (± 2.11) ng/ml, ranging from 1.8 to 16.7 pmol/l Mean

change from baseline at study end (Visit 6): 0.1 (± 1.53) pmol/l Mean

relative change from baseline: 4.7% (± 29.07%)

Overall, the change from baseline at study end was not significant in both, *t* test (test statistic: 0.89, d.f. 301, *p*=0.3764) as well as Wilcoxon's signed-rank test (test statistic: 662, *p*=0.6589).

No statistically remarkable differences between breast and prostate cancer patients were observed.

Mean (± S.D.) course of RANKL (ITT)

At baseline: 0.1 (± 0.27) pmol/l, ranging from 0.0 to 2.2 pmol/l

At study end: 0.1 (± 0.33) pmol/l, ranging from 0.0 to 3.0 pmol/l

Mean change from baseline at study end: 0.0 (± 0.31) pmol/l

Mean relative change from baseline: 123.4% (± 653.95%)

Overall, the change from baseline at study end was not significant in both, *t* test (test statistic: 0.04, d.f. 301, *p*=0.9648) as well as Wilcoxon's signed-rank test (test statistic: -243.5, *p*=0.6588)

No statistically remarkable differences between breast and prostate cancer patients were observed.

Secondary Objective Result(s)

Analgesics score

At Visit 1/Baseline: 185 (46.6%) of the patients: 'None'; 140 (35.3%) of 'Minor analgesics', 9 (2.3%) of 'Tranquillizers, antidepressants, muscle relaxants, and steroids', 32 (8.1%) of 'Mild narcotics', and 27 (6.8%) of 'Strong narcotics'. For 5 (1.3%) of the patients, the analgesic score was missing at baseline.

At study end (Visit 6): 166 (41.8%) 'None', 105 (26.4%) 'Minor analgesics', 3 (0.8%) 'Tranquillizers, antidepressants, muscle relaxants, and steroids', 28 (7.1%) 'Mild narcotics' and 43 (10.8%) 'Strong narcotics' (missing: 52 (13.1%))

Overall: increase in analgesic score compared to baseline was small, but significant (Bowker test, test statistic = 17.32, d.f. = 6.0, p = 0.0082)

Pearson and Spearman correlation coefficients for level of bone markers against VAS pain scores (ITT)

		Pearson		Spearman	
Parameter	N used	rho	p|rho=0	rho	p|rho=0
PINP [ng/ml]	1309	0.108	<0.0001	0.126	<0.0001
CTX [ng/ml]	1309	0.085	0.0021	0.112	<0.0001
OPG [pmol/l]	1309	0.074	0.0075	0.057	0.0403
RANKL [pmol/l]	1309	-0.0499	0.0710	-0.050	0.0691

Rate of skeletal related events (SRE)

In total: 11 (2.8%) (exact 95% CI: [1.4% ; 4.9%]) (starting after first dose of study drug, but not later than last dose of study drug)

Patients with SRE: 2 (0,5%), without: 387 (97.2%)

Quality of life (EORTC C-30):

Changes from baseline at Visit 6/Final Visit in EORTC C-30 (ITT)

a) EORTC C-30 Functional scale	n	Mean	SD	Median	p^a	p^b
Physical functioning	280	-2.7	19.43	0	0.0212	0.0183
Role functioning	278	-4.1	30.26	0	0.0255	0.0932
Emotional functioning	281	0.9	25.08	0	0.5659	0.3467
Cognitive functioning	281	-2.5	19.66	0	0.0346	0.0835
Social functioning	281	-2.6	28.14	0	0.1299	0.1874
Global health status / QoL	280	3.2	23.66	0	0.0265	0.0189
Fatigue	281	2.6	24.91	0	0.0779	0.0897
Nausea/Vomiting	281	2.3	19.99	0	0.0598	0.0301

Pain	281	-0.7	31.17	0	0.7022	0.6601
Dyspnoea	281	5.0	27.29	0	0.0024	0.0010
Insomnia	278	-1.0	35.02	0	0.6483	0.7771
Appetite loss	280	2.9	34.68	0	0.1691	0.1506
Constipation	280	3.1	29.03	0	0.0755	0.0943
Diarhoea	281	0.4	24.64	0	0.8089	0.7966
Financial problems	278	3.1	24.82	0	0.0371	0.0212

[a] *t* test, [b] Wilcoxon signed-rank test. Highlighted are scales with a signed-rank test $p < 0.05$

Course of PSA (Mean ± SD; patients with prostate cancer only)

At baseline: 168.5 (± 531.0) µg/l, ranging from 0.0 to 5000.0 µg/l

At study end: 92.5 (± 248.69) µg/l, ranging from 0.0 to 2328.0 µg/l

Mean change from baseline at study end: -52.6 (± 480.07) µg/l

Mean relative change from baseline: 68.9% (± 366.53%;)

Overall, the change from baseline at study end was not significant in both, *t* test (test statistic: -1.65, d.f. 246, p=0.0999) as well as Wilcoxon's signed-rank test (test statistic: -1078, p=0.2711;).

Safety Results

Adverse Events by System Organ Class

	Novartis product N (%)
Patients studied	
Randomized patients	400 (100)
Patients with drug-related AE	52 (13.0)

Drug-related AEs by primary system organ class

Preferred term	n	% of patients (n=400)
All System Organ Classes	51	(12.8)
CARDIAC DISORDERS	1	(0.3)
EAR AND LABYRINTH DISORDERS	1	(0.3)
EYE DISORDERS	3	(0.8)
GASTROINTESTINAL DISORDERS	11	(2.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	29	(7.3)
IMMUNE SYSTEM DISORDERS	1	(0.3)
INFECTIONS AND INFESTATIONS	1	(0.3)
INVESTIGATIONS	5	(1.3)
METABOLISM AND NUTRITION DISORDERS	4	(1.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	20	(5.0)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2	(0.5)

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

Preferred term	n	% of patients (n=400)
Bone pain	45	(11.3)
Nausea	33	(8.3)
Fatigue	25	(6.3)
Back pain	19	(4.8)
Constipation	18	(4.5)
Vomiting	18	(4.5)
Chills	18	(4.5)
Pain in extremity	18	(4.5)
Pyrexia	16	(4.0)
Diarrhoea	14	(3.5)

Serious Adverse Events and Deaths

	No. (%) of AEs	No. (%) of patients (n=400)
Serious AEs	154 (19.5)	75 (18.8)

Deaths		17 (4.3)
SAEs with suspected drug relation	7 (0.9)	4 (1.0)
SAEs leading to permanent discontinuation	11 (1.4)	10 (2.5)

Other Relevant Findings

N/A

Date of Clinical Trial Report

21 June 2010

Date Inclusion on Novartis Clinical Trial Results Database

18 August 2010

Date of Latest Update