Sponsor

Novartis

Generic Drug Name

Zoledronic acid

Therapeutic Area of Trial

Multiple myeloma with malignant bone lesion or breast cancer with bone metastases

Approved Indication

- Indicated for Treatment of hypercalcemia of malignancy (HCM) defined as albumin-corrected serum calcium (cCa) ≥12.0 mg/dL [3.0 mmol/L].
- Indicated for adjuvant treatment of hormone receptor-positive early breast cancer (EBC) in premenopausal women, in conjunction with hormonal therapy that includes a Gonadotropin Releasing Hormone (GnRH) agonist.
- Indicated for prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumor-induced hypercalcemia) in patients with advanced malignancies involving bone.
- Indicated for prevention of fracture and bone loss in postmenopausal women with early breast cancer (EBC) treated with aromatase inhibitors (AIs).
- Indicated for treatment of severe osteogenesis imperfecta (OI) in pediatric patients.

Protocol Number

CZOL446E2105

Title

A stratified, randomized, open-label, multi-center comparative 2-arm trial of pharmacokinetics (PK), pharmacodynamics (PD), and safety of Zometa® infusions administered monthly vs. every 3-month, in multiple myeloma patients with malignant bone lesions, and breast cancer patients with bone metastasis, who have received 9 to 12 doses of Zometa® over the prior year.

Phase of Development

Phase I

Study Start/End Dates

03-Nov-2006 (first patient first visit) to 20-Nov-2009 (Last patient last visit)

Study Design/Methodology

This was a 1-year, open-label, balanced, randomized, multi-dose, multi-center study in up to 36 cancer patients with multiple myeloma with malignant bone lesion or breast cancer with bone metastases who had been treated with 9 to 12 infusions of Zometa during the previous year. Due to a slower than expected recruitment rate, the protocol was amended to include

patients who had been treated with 9 to 20 infusions of Zometa during the previous 10 to 15 months. The study assessed and compared the PK, PD, and safety of Zometa administered intravenously every 4 weeks versus every 12 weeks.

Centres

Seven centers in United States.

Publication

None

Outcome measures

Primary outcome measure:

- Assessment of repeat-dose PK profile of zoledronic acid when administered every 4 weeks or every 12 weeks in patients treated with nine to 20 infusions of Zometa during the previous 10 to 15 months.

Secondary outcome measures:

- Assessment of skeletal related events (SRE) defined as pathologic bone fractures, spinal cord compression, surgery to bone, and radiation therapy to bone for efficacy.
- Safety profile of zoledronic acid.

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

Zometa IV infusion given over no less than 15 minutes every 4 or 12 weeks. Zometa was provided in plastic vials containing 4 mg zoledronic acid in a 5 mL concentrate for infusion. Individual patient doses were based on baseline creatinine clearance (CLcr).

Statistical Methods

The analysis of this study was conducted using SAS® software version 9.1 (or higher) (SAS Institute, Inc, Cary, North Carolina). The individual plasma and urine concentrations were summarized with descriptive statistics. Non-compartmental PK parameters characterizing the disposition of zoledronic acid were derived from the individual plasma concentration-time profiles, using non-compartmental method(s) using WinNonlin® Professional (Pharsight, St. Louis, Missouri). Summary tables were generated for the entire study population and for each cancer type (multiple myeloma or breast cancer) by treatment arm. Log-transformed PK parameter (AUC0-24h, Cend, Ae0-24h [% of dose]) ratios from Day 1 to Months 3 and 6 were modeled by a linear mixed-effect model including the treatment (Zometa every 4 weeks and Zometa every 12 weeks), the month (3 and 6), and the cancer type as fixed effects, and the 2-way treatment-by-month interaction. The difference between the two treatment arms averaged across Months 3 and 6 and its 90% confidence interval (CI) was calculated from the model and were back-transformed to obtain the between-treatment geometric mean ratio (Zometa every 4 weeks treatment group divided by Zometa every 12 weeks treatment group, with respect to the [log-transformed] PK parameter ratios averaged across Months 3 and 6) and the corresponding 90% CI to test for any difference. The difference between the two treatment arms was similarly estimated at individual levels of Months 3 and 6.

Listings were sorted by treatment, cancer type first, then sorted by country, center, and

patient ID within each cancer type. For PK and PD analyses, data were summarized by the nominal visits recorded on the case report form.

Study Population:

Inclusion Criteria

Patients were eligible for inclusion if they met all of the following criteria:

- Signed informed consent, obtained prior to any screening procedures that were not standard of care or unless otherwise noted
- Male or female between 18 and 75 years of age
- Cancer diagnosis of
- Multiple myeloma and at least one demonstrable osteolytic bone lesion (radiologically confirmed; bone scintigraphy as sole diagnostic criterion not acceptable)

Or

- Stage IV breast cancer patients with at least one bone metastasis (radiologically confirmed; bone scintigraphy as sole diagnostic criterion not acceptable)
- Zometa treatment history (all of the following three criteria were to be met):
- Initiation of Zometa treatment for bone lesions between 10 to 15 months prior to randomization, and
- A total of nine to 20 infusions of Zometa had been received, and
- Last infusion of Zometa occurred within ≤ 60 days of randomization
- Life expectancy of ≥ 1 year
- Eastern Cooperative Oncology Group (ECOG) status of 0, 1, or 2

Exclusion Criteria

Patients were to be excluded from participation if they met any of the following criteria:

- Laboratory values of:
  - Documented serum creatinine >3 mg/dL (265 µmol/L) within 9 to 12 months of randomization
  - Documented calculated creatinine clearance (according to Cockcroft and Gault 1976) <30 mL/min within 9 to 12 months of randomization
  - Corrected serum calcium of ≤ 8.0 mg/dL (2.0 mmol/L) or >12 mg/dL (3.0 mmol/L)
  - A local serum creatinine at Baseline (Visit 2) that meets any of the criteria outlined below. Patients did not undergo screening again if their local serum creatinine value met the recovery criteria defined below and the 27 day screening window was not exceeded

    following information was to be available prior to randomization:

    - *De novo* serum creatinine (before first-ever dose of Zometa). The *de novo* serum creatinine was used as the reference value for dose interruptions in the present study.
    - Serum creatinine before each of the 9 to 20 doses of Zometa received prior to

enrollment in the present study. Patients with an incomplete record of serum creatinine measurements could be enrolled if, following discussion between the investigator and Novartis, it was determined that the absence of such data did not pose a risk to the patient when enrolled into the study.

- Diagnosis of metabolic bone disorders other than osteoporosis (e.g. Paget's disease)
- 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 8 weeks) or planned dental or jaw surgery (e.g. extraction, implants)
- Active or uncontrolled infection
- Acute or chronic liver or renal disease
- History of treatment with iv bisphosphonates other than Zometa
- Patients treated with oral bisphosphonates <1 year prior to randomization
- Treatment with calcitonin, gallium nitrate, or mithramycin within 14 days prior to study drug administration
- Pregnant patients (who had a positive pregnancy test prior to study entry) or lactating patients. Patients of reproductive potential not using effective methods of birth control (e.g. abstinence, oral contraceptives or implants, intra-uterine device, vaginal diaphragm or sponge, or condom with spermicide). Patients of childbearing potential required a negative pregnancy test at Visit 1 (Screening Visit)

Participant Flow

Patient disposition (ITT data set)

	Zometa every 4 weeks (N=9) n (%)	Zometa every 12 weeks (N=9) n (%)	Total (N=18) n (%)
Total number of patients			
Not treated	0	0	0
Treated	9 (100.0)	9 (100.0)	18 (100.0)
Completed treatment	7 (77.8)	7 (77.8)	14 (77.8)
Discontinued treatment	2 (22.2)	2 (22.2)	4 (22.2)
Primary reason for treatment discontinuation			
Adverse event(s)	0	1 (11.1)	1 (5.6)
Abnormal test procedure result(s)	1 (11.1)	0	1 (5.6)
Patient withdrew consent	1 (11.1)	0	1 (5.6)
Disease progression	0	1 (11.1)	1 (5.6)

ITT: intent to treat

Demographic and other baseline characteristics

Demographic and baseline characteristics (ITT data set)

		Zometa every 4 weeks (N=9)	Zometa every 12 weeks (N=9)	Total (N=18)
Age (years)	n	9	9	18
	Mean (SD)	58.6 (14.13)	58.1 (10.37)	58.3 (12.02)
	Median	62.0	60.0	61.0
	Min-Max	31, 75	40, 71	31, 75
Age group n (%)	≤65 years	6 (66.7)	6 (66.7)	12 (66.7)
	>65 years	3 (33.3)	3 (33.3)	6 (33.3)
Gender (%)	Male	2 (22.2)	3 (33.3)	5 (27.8)
	Female	7 (77.8)	6 (66.7)	13 (72.2)
Predominant race n (%)	Caucasian	9 (100.0)	9 (100.0)	18 (100.0)
Ethnicity n (%)	Other	9 (100.0)	9 (100.0)	18 (100.0)
Source of patient referral n (%)	Physician's own practice	7 (77.8)	9 (100.0)	16 (88.9)
	Physician referral	2 (22.2)	0	2 (11.1)
Weight (kg)	n	9	9	18
	Mean (SD)	67.32 (12.044)	78.12 (9.406)	72.72 (11.865)
	Median	63.10	81.40	71.25

	Min-Max	56.8, 96.8	59.5, 89.1	56.8, 96.8
Height (cm)	n	9	9	18
	Mean (SD)	164.6 (10.01)	167.6 (8.82)	166.1 (9.28)
	Median	165.0	165.0	165.0
	Min-Max	154, 188	156, 180	154, 188
Body mass index (kg/m^2)	n	9	9	18
	Mean (SD)	24.72 (2.064)	27.94 (3.920)	26.33 (3.462)
	Median	25.41	25.69	25.61
	Min-Max	21.7, 27.4	23.2, 33.9	21.7, 33.9
Cancer type n (%)	Multiple myeloma	3 (33.3)	4 (44.4)	7 (38.9)
	Breast cancer	6 (66.7)	5 (55.6)	11 (61.1)
Baseline serum creatinine (mg/dL) [a]	n	9	9	18
	Mean (SD)	0.98 (0.109)	0.96 (0.188)	0.97 (0.150)
	Median	1.00	1.00	1.00
	Min-Max	0.8, 1.1	0.7, 1.3	0.7, 1.3
Baseline creatinine clearance	Mean (SD)	72.22 (21.58)	86.22 (25.36)	
***De novo* renal function** [b] n (%)	Normal	9 (100.0)	8 (88.9)	17 (94.4)
	Abnormal	0	1 (11.1)	1 (5.6)

ITT: intent to treat; Max: maximum; Min: minimum; SD: standard deviation.

[a] Baseline serum creatinine was defined as the patient's last serum creatinine reported prior to randomization.

[b] A *de novo* serum creatinine level of ≤ 1.4 mg/dL was considered normal. Otherwise, it was classified as abnormal. *De novo* serum creatinine level was defined as the serum creatinine level just prior to the first-ever Zometa dose, approximately 1 year prior to study entry.

Disease characteristics by treatment group (ITT data set)

		Zometa every 4 weeks (N=9)	Zometa every 12 weeks (N=9)	Total (N=18)
Multiple myeloma				
Number of patients with multiple myeloma n (%)		3 (33.3)	4 (44.4)	7 (38.9)
Stage at initial diagnosis n (%) [a]	Stage I	2 (66.7)	2 (50.0)	4 (57.1)
	Stage II	0	0	0
	Stage III	1 (33.3)	1 (25.0)	2 (28.6)
	Unknown	0	1 (25.0)	1 (14.3)
Months since initial diagnosis [b]	n	3	4	7
	Mean (SD)	14.29 (6.275)	82.93 (137.659)	53.51 (104.087)
	Median	10.80	15.18	14.93
	Min-Max	10.5 - 21.5	11.9, 289.4	10.5, 289.4
Months since first bone metastasis diagnosis [b]	n	3	4	7
	Mean (SD)	14.28 (6.285)	12.90 (1.371)	13.49 (3.828)
	Median	10.80	12.37	12.37
	Min-Max	10.5, 21.5	11.9, 14.9	10.5, 21.5
Breast cancer				

Number of patients with breast cancer n (%)		6 (66.7)	5 (55.6)	11 (61.1)
Stage at initial diagnosis n (%) [c]	Stage I	0	2 (40.0)	2 (18.2)
	Stage IIa	2 (33.3)	0	2 (18.2)
	Stage IIb	2 (33.3)	2 (40.0)	4 (36.4)
	Stage IIIa	0	0	0
	Stage IIIb	0	1 (20.0)	1 (9.1)
	Stage IV	0	0	0
	Unknown	2 (33.3)	0	2 (18.2)
Months since initial diagnosis [b]	n	6	5	11
	Mean (SD)	94.02 (53.319)	93.34 (74.788)	93.71 (60.489)
	Median	90.37	59.10	65.23
	Min-Max	29.5, 178.3	24.1, 215.5	24.1, 215.5
Months since first metastasis diagnosis [b]	n	6	5	11
	Mean (SD)	11.96 (1.545)	26.07 (21.716)	18.37 (15.623)
	Median	11.77	11.07	11.47
	Min-Max	10.0, 14.0	9.9, 52.8	9.9, 52.8

ITT: intent to treat; Max: maximum; Min: minimum; SD: standard deviation.
[a] Number of patients with multiple myeloma was used as denominator to calculate percentage.
[b] Time since event in months was defined as (the screening assessment date – event date + 1)/30.
[c] Number of patients with breast cancer was used as denominator to calculate percentage.

Outcome measures

Primary Outcome Result(s)

Summary statistics for plasma zoledronic acid pharmacokinetic parameters (Plasma PK data set)

	Zometa every 4 weeks (N=9)	Zometa every 12 weeks (N=9)
Day 1		
AUC0-24h (h.ng/mL)		
n	9	9
Mean (SD)	475.97 (137.04)	399.633 (99.79)
CV% mean	28.79	24.97
Geo-mean	454.74	386.93
CV% geo-mean	35.005	28.76
Median	502.985	405.37
Min, Max	219.82, 639.60	211.50, 565.47
Cend (ng/mL)		
n	9	9
Mean (SD)	243.11 (70.56)	209.333 (131.70)
CV% mean	29.02	62.91
Geo-mean	234.13	188.11
CV% geo-mean	29.90	45.43
Median	231.00	169.00
Min, Max	141.00, 367.00	117.00, 555.00

CL (L/h)		
n	5	5
Mean (SD)	8.85 (6.06)	11.56 (3.53)
CV% mean	68.52	30.59
Geo-mean	7.01	11.17
CV% geo-mean	95.87	29.04
Median	8.93	9.52
Min, Max	2.49, 17.36	8.69, 17.11
CLcr (mL/min)		
n	9	9
Mean (SD)	72.22 (21.58)	86.22 (25.36)
CV% mean	29.88	29.42
Geo-mean	69.56	82.86
CV% geo-mean	29.29	30.96
Median	71.33	92.33
Min, Max	49.00, 115.00	49.00, 131.33
Month 3		
AUC0-24h (h.ng/mL)		
n	6	8
Mean (SD)	801.69 (892.65)	464.15 (223.52)
CV% mean	111.34	48.15
Geo-mean	580.30	407.23
CV% geo-mean	89.35	64.60
Median	429.18	440.79
Min, Max	356.18, 2612.32	131.07, 742.87
Cend (ng/mL)		
n	6	8
Mean (SD)	654.00 (818.69)	393.250 (436.0265)
CV% mean	125.18	110.87
Geo-mean	377.79	272.27
CV% geo-mean	146.84	100.06
Median	198.00	214.00
Min, Max	185.00, 2210.00	110.00, 1400.00
CL (L/h)		
n	2	5
Mean (SD)	8.61 (3.26)	9.118 (3.59)
CV% mean	37.94	39.47
Geo-mean	8.29	8.51
CV% geo-mean	40.41	44.43
Median	8.61	9.72
Min, Max	6.30, 10.92	5.04, 13.58
CLcr (mL/min)		
n	6	8
Mean (SD)	69.22 (27.01)	81.500 (22.50)
CV% mean	39.03	27.61

Geo-mean	65.54	78.90
CV% geo-mean	36.03	27.67
Median	61.50	78.33
Min, Max	47.33, 119.00	50.00, 125.00
Month 6		
AUC0-24h (h.ng/mL)		
n	7	8
Mean (SD)	405.33 (120.58)	405.694 (146.89)
CV% mean	29.74	36.20
Geo-mean	390.07	375.97
CV% geo-mean	30.70	47.76
Median	409.25	413.75
Min, Max	272.98, 584.21	143.98, 601.26
Cend (ng/mL)		
n	7	8
Mean (SD)	185.60 (79.23)	181.25 (45.86)
CV% mean	42.68	25.30
Geo-mean	165.14	175.95
CV% geo-mean	62.65	26.93
Median	218.00	177.00
Min, Max	62.40, 270.00	112.00, 246.00
CL (L/h)		
n	2	7
Mean (SD)	7.73 (6.10)	11.369 (7.30)
CV% mean	79.03	64.21
Geo-mean	6.41	9.46
CV% geo-mean	110.37	78.63
Median	7.73	9.26
Min, Max	3.41, 12.05	2.58, 26.16
CLcr (mL/min)		
n	7	8
Mean (SD)	67.83 (23.99)	82.729 (23.31)
CV% mean	35.36	28.18
Geo-mean	64.73	80.19
CV% geo-mean	32.85	26.43
Median	59.33	78.50
Min, Max	45.50, 115.00	58.33, 130.67

AUC0-24h: area under the concentration-time curve from time zero to 24 hours; Cend: plasma drug concentration, typically the maximum (peak) at the end of an infusion; CL: total body clearance of drug from the plasma; CLcr: creatinine clearance; CV: coefficient of variation; Geo: geometric; Max: maximum; Min: minimum; PK: pharmacokinetic; SD: standard deviation.

Note: CV% = coefficient of variation (%) = SD/mean × 100.

CV% geo-mean = √(exp (variance for log-transformed data) – 1) × 100.

1 month = 4 weeks

Statistical analysis of plasma zoledronic acid pharmacokinetic parameter ratios:

comparison between treatment groups (Plasma PK data set)

Parameter	Treatment	n	Adjusted geometric mean	Treatment comparison: Geometric mean ratio[a]	90% CI: Lower	90% CI: Upper
Average over Months 3 and 6						
AUC0-24h (h.ng/mL)	A	7	1.05			
	B	9	1.00	1.05	0.77	1.43
Cend (ng/mL)	A	7	1.05			
	B	9	1.21	0.87	0.56	1.35
Month 3						
AUC0-24h (h.ng/mL)	A	6	1.30			
	B	8	0.98	1.33	0.86	2.04
Cend (ng/mL)	A	6	1.63			
	B	8	1.38	1.18	0.61	2.31
Month 6						
AUC0-24h (h.ng/mL)	A	7	0.84			
	B	8	1.02	0.83	0.55	1.24
Cend (ng/mL)	A	7	0.67			
	B	8	1.06	0.64	0.34	1.20

AUC0-24h: area under the concentration-time curve from time zero to 24 hours; Cend: plasma drug concentration, typically the maximum (peak) at the end of an infusion; CL: total body clearance of drug from the plasma; CLcr: creatinine clearance; PK: pharmacokinetic

[a] Geometric mean ratio is A/B

Note: Treatment A = Zometa every 4 weeks; Treatment B = Zometa every 12 weeks; n = number of patients with non-missing values; 1 month = 4 weeks.

Model was a linear mixed-effects model of the log-transformed PK parameter ratios from Day 1 to Months 3 and 6. Included in the model were treatment (A and B), Month (3 and 6), and cancer type as fixed effects and the 2-way treatment-by-month interaction. The variability of the residuals at Months 3 and 6 was modeled by means of a first-order autoregressive correlation structure.

Summary statistics for urine zoledronic acid pharmacokinetic parameters (Urine PK data set)

	Zometa every 4 weeks (N=7)	Zometa every 12 weeks (N=8)
Day 1		
Ae0-24h (mg)		
n	6	6
Mean (SD)	1.46 (0.81)	2.020 (1.65)
CV% mean	56.00	82.12
Geo-mean	1.23	1.45
CV% geo-mean	75.87	120.90
Median	1.48	1.94
Min, Max	0.53, 2.35	0.41, 4.99
Ae0-24h (% of dose)		
n	6	6
Mean (SD)	36.50 (20.44)	50.48 (41.45)

CV% mean	56.00	82.11
Geo-mean	30.86	36.34
CV% geo-mean	75.87	120.86
Median	37.20	48.61
Min, Max	13.18, 58.80	10.26, 124.75
CLr (mL/min)		
n	6	6
Mean (SD)	56.35 (23.87)	89.43 (66.82)
CV% mean	42.36	74.71
Geo-mean	49.89	69.32
CV% geo-mean	67.87	97.91
Median	62.37	86.73
Min, Max	15.43, 77.93	21.91, 209.39
Dose (mg)		
n	6	6
Mean (SD)	4.00 (0.00)	4.00 (0.00)
CV% mean	0.00	0.00
Geo-mean	4.00	4.00
CV% geo-mean	0.00	0.00
Median	4.00	4.00
Min, Max	4.0, 4.0	4.0, 4.0
Month 3		
Ae0-24h (mg)		
n	6	5
Mean (SD)	1.42 (0.74)	1.765 (0.81)
CV% mean	52.21	46.43
Geo-mean	1.29	1.59
CV% geo-mean	49.32	55.25
Median	1.29	1.71
Min, Max	0.78, 2.82	0.79, 2.73
Ae0-24h (% of dose)		
n	6	5
Mean (SD)	35.66 (18.62)	44.11 (20.48)
CV% mean	52.21	46.43
Geo-mean	32.37	39.95
CV% geo-mean	49.31	55.25
Median	32.25	42.96
Min, Max	19.44, 70.60	19.74, 68.21
CLr (mL/min)		
n	5	5
Mean (SD)	45.80 (16.44)	78.404 (34.42)
CV% mean	35.89	43.90
Geo-mean	42.99	70.16
CV% geo-mean	43.86	63.21

Median	50.75	88.72
Min, Max	22.41, 63.45	26.97, 113.68
Dose (mg)		
n	6	5
Mean (SD)	4.00 (0.00)	4.00 (0.00)
CV% mean	0.00	0.00
Geo-mean	4.00	4.00
CV% geo-mean	0.00	0.00
Median	4.00	4.00
Min, Max	4.0, 4.0	4.0, 4.0
Month 6		
Ae0-24h (mg)		
n	6	7
Mean (SD)	1.54 (0.76)	1.80 (1.06)
CV% mean	49.13	59.35
Geo-mean	1.32	1.56
CV% geo-mean	80.07	61.33
Median	1.78	1.49
Min, Max	0.36, 2.54	0.84, 3.50
Ae0-24h (% of dose)		
n	6	7
Mean (SD)	38.71 (19.01)	45.03 (26.73)
CV% mean	49.13	59.36
Geo-mean	33.01	39.09
CV% geo-mean	80.06	61.35
Median	44.64	37.37
Min, Max	9.03, 63.58	20.93, 87.44
CLr (mL/min)		
n	6	7
Mean (SD)	57.24 (19.57)	88.06 (62.09)
CV% mean	34.20	70.50
Geo-mean	53.15	71.48
CV% geo-mean	49.65	78.88
Median	61.64	75.30
Min, Max	21.23, 74.15	33.66, 196.52
Dose (mg)		
n	6	7
Mean (SD)	4.00 (0.00)	4.00 (0.00)
CV% mean	0.00	0.00
Geo-mean	4.00	4.00
CV% geo-mean	0.00	0.00
Median	4.00	4.00
Min, Max	4.0, 4.0	4.0, 4.0

Ae0-24h: amount of unchanged drug excreted into the urine from time zero to 24 hours; Ae0-24h (% of dose): percent of unchanged drug excreted into the urine from time zero to 24 hours over dose amount; CLr: renal clearance of drug from the plasma; CV: coefficient of variation; Geo: geometric; Max: maximum; Min: minimum; PK: pharmacokinetic; SD: standard deviation.

Note: CV% = coefficient of variation (%) = SD/mean × 100.

CV% geo-mean = √(exp (variance for log-transformed data) – 1) × 100.

1 month = 4 weeks

Statistical analysis of urine zoledronic acid pharmacokinetic parameter ratios: comparison between treatment groups (Urine PK data set)

Parameter	Treatment	n	Adjusted geometric mean	Treatment comparison		
				Geometric mean ratio[a]	90% CI	
					Lower	Upper
Average over Months 3 and 6						
Ae0-24h (% of dose)	A	5	1.15			
	B	6	0.98	1.18	0.52	2.72
Month 3						
Ae0-24h (% of dose)	A	5	1.18			
	B	4	0.85	1.39	0.55	3.52
Month 6						
Ae0-24h (% of dose)	A	5	1.12			
	B	6	1.12	1.01	0.42	2.42

Ae0-24h: amount of unchanged drug excreted into the urine from time zero to 24 hours; PK: pharmacokinetic

[a] Geometric mean ratio is A/B

Note: Treatment A = Zometa every 4 weeks; Treatment B = Zometa every 12 weeks; n = number of patients with non-missing values; 1 month = 4 weeks.

Model was a linear mixed-effects model of the log-transformed PK parameter ratios from Day 1 to Months 3 and 6. Included in the model were treatment (A and B), Month (3 and 6), and cancer type as fixed effects and the 2-way treatment-by-month interaction. The variability of the residuals at Months 3 and 6 was modeled by means of a first-order autoregressive correlation structure.

Secondary Outcome Result(s)

Proportion of patients who experienced any skeletal-related event and each individual type of skeletal-related event during the study (ITT data set)

	Zometa every 4 weeks (N=9) n (%)	Zometa every 12 weeks (N=9) n (%)	Total (N=18) n (%)
Number of patients with at least one SRE measurement	9 (100.0)	9 (100.0)	18 (100.0)
Number of patients with at least one SRE:			
Overall SRE including HCM [a]	1 (11.1)	2 (22.2)	3 (16.7)
Overall SRE excluding HCM [a]	1 (11.1)	2 (22.2)	3 (16.7)
Individual SRE:			
Pathologic fractures - vertebral	0	0	0
Pathologic fractures – non-vertebral	1 (11.1)	1 (11.1)	2 (11.1)
Spinal cord compression	0	0	0
Radiation to bone	0	1 (11.1)	1(5.6)
Surgery to bone	0	0	0
HCM [a]	0	0	0

HCM: hypercalcemia of malignancy; ITT: intent to treat; SRE: skeletal-related event
[a] HCM was defined as a corrected serum calcium ≥ 12.0 mg/dL.

Safety Results

Overall summary of adverse events regardless of study drug relationship by system organ class (Safety data set)

	Zometa every 4 weeks (N=9) n (%)	Zometa every 12 weeks (N=9) n (%)	Total (N=18) n (%)
Number of patients with at least one adverse event	9 (100.0)	9 (100.0)	18 (100.0)
Blood and lymphatic system disorders	5 (55.6)	2 (22.2)	7 (38.9)
Ear and labyrinth disorders	0	1 (11.1)	1 (5.6)
Eye disorders	2 (22.2)	2 (22.2)	4 (22.2)
Gastrointestinal disorders	6 (66.7)	4 (44.4)	10 (55.6)
General disorders and administration site conditions	4 (44.4)	5 (55.6)	9 (50.0)
Immune system disorders	1 (11.1)	0	1 (5.6)
Infections and infestations	4 (44.4)	5 (55.6)	9 (50.0)

Injury, poisoning, and procedural complications	3 (33.3)	0	3 (16.7)
Investigations	2 (22.2)	1 (11.1)	3 (16.7)
Metabolism and nutrition disorders	2 (22.2)	3 (33.3)	5 (27.8)
Musculoskeletal and connective tissue disorders	7 (77.8)	5 (55.6)	12 (66.7)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (11.1)	2 (22.2)	3 (16.7)
Nervous system disorders	5 (55.6)	4 (44.4)	9 (50.0)
Psychiatric disorders	4 (44.4)	3 (33.3)	7 (38.9)
Renal and urinary disorders	2 (22.2)	2 (22.2)	4 (22.2)
Reproductive system and breast disorders	1 (11.1)	0	1 (5.6)
Respiratory, thoracic, and mediastinal disorders	4 (44.4)	4 (44.4)	8 (44.4)
Skin and subcutaneous tissue disorders	6 (66.7)	4 (44.4)	10 (55.6)
Surgical and medical procedures	0	1 (11.1)	1 (5.6)
Vascular disorders	1 (11.1)	3 (33.3)	4 (22.2)

Note: Adverse events were coded using MedDRA Version 14.1.
A patient was counted once if the patient reported one or more events with the same system organ class.
Only treatment-emergent adverse events are included in the summary. Treatment-emergent adverse events were defined as adverse events with onset dates on or after the date of the first dose of the study medication and within 28 days after the date of the last dose of the study medication, or were present before treatment but worsened during treatment.

Summary of frequent (≥10%) adverse events regardless of study drug relationship by preferred term (Safety data set)

	Zometa every 4 weeks (N=9) n (%)	**Zometa every 12 weeks (N=9) n (%)**	**Total (N=18) n (%)**
Number of patients with at least one adverse event	9 (100.0)	9 (100.0)	18 (100.0)
Nausea	4 (44.4)	4 (44.4)	8 (44.4)
Fatigue	3 (33.3)	4 (44.4)	7 (38.9)
Pain in extremity	4 (44.4)	2 (22.2)	6 (33.3)
Vomiting	4 (44.4)	2 (22.2)	6 (33.3)
Back pain	3 (33.3)	2 (22.2)	5 (27.8)
Diarrhea	3 (33.3)	2 (22.2)	5 (27.8)
Insomnia	3 (33.3)	2 (22.2)	5 (27.8)
Anemia	2 (22.2)	2 (22.2)	4 (22.2)
Constipation	3 (33.3)	1 (11.1)	4 (22.2)
Decreased appetite	1 (11.1)	3 (33.3)	4 (22.2)
Headache	2 (22.2)	2 (22.2)	4 (22.2)

Alopecia	2 (22.2)	1 (11.1)	3 (16.7)
Arthralgia	2 (22.2)	1 (11.1)	3 (16.7)
Depression	1 (11.1)	2 (22.2)	3 (16.7)
Dizziness	1 (11.1)	2 (22.2)	3 (16.7)
Hypoesthesia	1 (11.1)	2 (22.2)	3 (16.7)
Musculoskeletal pain	2 (22.2)	1 (11.1)	3 (16.7)
Neutropenia	3 (33.3)	0	3 (16.7)
Edema peripheral	0	3 (33.3)	3 (16.7)
Paraesthesia	1 (11.1)	2 (22.2)	3 (16.7)
Pruritus	1 (11.1)	2 (22.2)	3 (16.7)
Rash	1 (11.1)	2 (22.2)	3 (16.7)
Vision blurred	1 (11.1)	2 (22.2)	3 (16.7)
Abdominal pain	0	2 (22.2)	2 (11.1)
Blood alkaline phosphatase increased	1 (11.1)	1 (11.1)	2 (11.1)
Cough	1 (11.1)	1 (11.1)	2 (11.1)
Eye irritation	1 (11.1)	1 (11.1)	2 (11.1)
Gastroenteritis	1 (11.1)	1 (11.1)	2 (11.1)
Metastases to central nervous system	1 (11.1)	1 (11.1)	2 (11.1)
Muscle spasms	1 (11.1)	1 (11.1)	2 (11.1)
Palmar-plantar erythrodysesthesia syndrome	2 (22.2)	0	2 (11.1)
Sinus congestion	1 (11.1)	1 (11.1)	2 (11.1)
Syncope	1 (11.1)	1 (11.1)	2 (11.1)
Upper respiratory tract infection	0	2 (22.2)	2 (11.1)

Note: Adverse events were coded using MedDRA Version 14.1.
Adverse events occurring in ≥ 10% of all patients in the total column are included.
A patient was counted once if the patient reported one or more events with the same preferred term.
Only treatment-emergent adverse events were included in the summary. Treatment-emergent adverse events were defined as adverse events with onset dates on or after the date of the first dose of the study medication and within 28 days after the date of the last dose of the study medication, or present before treatment but worsened during treatment.

Serious Adverse Events and Deaths

Summary of serious adverse events regardless of study drug relationship by system organ class and preferred term (Safety data set)

	Zometa every 4 weeks (N=9) n (%)	Zometa every 12 weeks (N=9) n (%)	Total (N=18) n (%)
Number of patients with at least one serious adverse event	1 (11.1)	2 (22.2)	3 (16.7)
Gastrointestinal disorders	1 (11.1)	1 (11.1)	2 (11.1)

Abdominal pain	0	1 (11.1)	1 (5.6)
Nausea	1 (11.1)	0	1 (5.6)
Vomiting	1 (11.1)	0	1 (5.6)
Infections and infestations	1 (11.1)	0	1 (5.6)
Pneumonia	1 (11.1)	0	1 (5.6)
Musculoskeletal and connective tissue disorders	0	1 (11.1)	1 (5.6)
Back pain	0	1 (11.1)	1 (5.6)
Nervous system disorders	0	1 (11.1)	1 (5.6)
Syncope	0	1 (11.1)	1 (5.6)
Psychiatric disorders	1 (11.1)	0	1 (5.6)
Mental status changes	1 (11.1)	0	1 (5.6)
Renal and urinary disorders	0	1 (11.1)	1 (5.6)
Hydronephrosis	0	1 (11.1)	1 (5.6)
Ureteric haemorrhage	0	1 (11.1)	1 (5.6)

Note: Adverse events were coded using MedDRA Version 14.1.
At each level of patient summarization, a patient was counted once if the patient reported one or more events.
Only treatment emergent adverse events were included in the summary. Treatment-emergent adverse events were defined as adverse events with onset dates on or after the date of the first dose of the study medication and within 28 days after the date of the last dose of the study medication, or were present before treatment but worsened during treatment.

Summary of deaths and adverse events - Safety data set

	Zometa every 4 weeks (N=9) n (%)	Zometa every 12 weeks (N=9) n (%)	Total (N=18) n (%)
Death	0	0	0
Osteonecrosis of the jaw[1]	1 (11.1)	0	1 (11.1)
Renal function deterioration[2]	1 (11.1)	2 (22.2)	3 (16.7)

[1] Confirmed cases

[2] A patient was categorized as having experienced renal function deterioration if the patient met one of the following criteria:

- An increase of serum creatinine of 0.5 mg/dL or more if the *de novo* serum creatinine level was normal (≤ 1.4 mg/dL);
- An increase of serum creatinine of 1.0 mg/dL or more if the *de novo* serum creatinine level was abnormal (>1.4 mg/dL);
- Doubling (or greater increase) of the serum creatinine level compared with the *de novo* level regardless of the categorization of the *de novo* serum creatinine level.

Number (%) of patients with newly occurring or worsening hematology abnormalities

Notable abnormality	Worsening from baseline to	Zometa every 4 weeks (N=9)	Zometa every 12 weeks (N=9)

		Total	n (%)	Total	n (%)
Absolute neutrophils	Grade 1	8	0	8	0
	Grade 2	8	2 (25.0)	8	0
	Grade 3	8	2 (25.0)	8	0
	Grade 4	8	0	8	0
Hemoglobin	Grade 1	8	1 (12.5)	6	2 (33.3)
	Grade 2	8	3 (37.5)	8	1 (12.5)
	Grade 3	9	1 (11.1)	9	0
	Grade 4	9	0	9	0
Platelet count	Grade 1	9	1 (11.1)	9	0
	Grade 2	9	0	9	0
	Grade 3	9	0	9	0
	Grade 4	9	0	9	0
WBC (total)	Grade 1	5	0	9	3 (33.3)
	Grade 2	9	5 (55.6)	9	0
	Grade 3	9	0	9	0
	Grade 4	9	0	9	0

WBC: white blood cell

Note: Total = number of patients evaluable post-baseline, who had less than grade x at baseline. This number was used as denominator to calculate percentage.

n = number of patients who had less than grade x at baseline, and worsened to grade x post-baseline.

Number (%) of patients with newly occurring or worsening biochemistry abnormalities

Notable abnormality	Worsening from baseline to	Zometa every 4 weeks (N=9)		Zometa every 12 weeks (N=9)	
		Total	n (%)	Total	n (%)
Alkaline phosphate	Grade 1	7	2 (28.6)	7	1 (14.3)
	Grade 2	8	2 (25.0)	9	1 (11.1)
	Grade 3	9	0	9	0
	Grade 4	9	0	9	0
Bilirubin (total)	Grade 1	8	0	9	3 (33.3)
	Grade 2	9	0	9	0
	Grade 3	9	0	9	0
	Grade 4	9	0	9	0
Corrected calcium	Grade 1	2	0	4	0
	Grade 2	2	0	4	0
	Grade 3	2	0	4	0
	Grade 4	2	0	4	0
Creatinine	Grade 1	9	9 (100.0)	9	8 (88.9)
	Grade 2	9	0	9	0
	Grade 3	9	0	9	0
	Grade 4	9	0	9	0
Magnesium	Grade 1	5	4 (80.0)	7	2 (28.6)
	Grade 2	9	0	9	0

	Grade 3	9	1	9	1 (11.1)
	Grade 4	9	1 (11.1)	9	0
Phosphate	Grade 1	9	0	9	0
	Grade 2	9	1 (11.1)	9	2 (22.2)
	Grade 3	9	1 (11.1)	9	1 (11.1)
	Grade 4	9	0	9	0
Potassium	Grade 1	9	3 (33.3)	8	1 (12.5)
	Grade 2	9	1 (11.1)	9	0
	Grade 3	9	0	9	0
	Grade 4	9	0	9	0
AST	Grade 1	5	4 (80.0)	6	2 (33.3)
	Grade 2	9	1 (11.1)	9	2 (22.2)
	Grade 3	9	0	9	0
	Grade 4	9	0	9	0
ALT	Grade 1	7	2 (28.6)	8	3 (37.5)
	Grade 2	9	1 (11.1)	9	0
	Grade 3	9	0	9	0
	Grade 4	9	0	9	0
Sodium	Grade 1	9	1 (11.1)	9	0
	Grade 2	9	0	9	0
	Grade 3	9	0	9	1 (11.1)
	Grade 4	9	0	9	0

ALT: alanine aminotransferase; AST: aspartate aminotransferase

Note: Total = number of patients evaluable post-baseline, who had less than grade x at baseline. This number was used as denominator to calculate percentage.

n = number of patients who had less than grade x at baseline, and worsened to grade x post-baseline.

Other Relevant Findings

None

Date of Clinical Trial Report

12-Sep-2012

Date Inclusion on Novartis Clinical Trial Results Database

19-Nov-2012

Date of Latest Update