Sponsor

Novartis

Generic Drug Name

Zoledronic acid

Therapeutic Area of Trial

Breast cancer, prostrate cancer

Approved Indication

Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone. Treatment of tumour-induced hypercalcaemia (TIH).

Study Number

CZOL446EHU03

Title

A multicenter, open-label study to assess effect of I.V Zometa on pain and quality of life in patients with bone metastases with or without skeletal related events (SREs) resulting from breast cancer and prostrate cancer

Phase of Development

IV

Study Start/End Dates

12 July 2005 to 30 April 2008

Study Design/Methodology

This was a prospective, open-label, multi-center study. A 4 mg dose of zoledronic acid was administered, as an intravenous (i.v) infusion for at least 15 min, every 3-4 weeks for a maximum of 6 infusions. Each patient's duration of participation was up to 28 weeks, including a four week screening period, a 15 to 20-week treatment period, and 4-week follow-up.

Twenty-eight days following the last infusion, a final safety visit was performed.

Centers

6 study centers in Hungary.

Publication

None

Objectives

Primary objective(s)

The primary objective of this study was to assess pain course over time measured by a visual analog scale (VAS).

- Patients who reported pain upon entry into the trial were evaluated for their course of pain.
- Patients who did not have pain upon entry into the trial were be evaluated for time to onset of pain.

Secondary objective(s)

The secondary objectives of this trial include time in chair (infusion time), quality of life (Functional Assessment of Cancer Therapy Scale – General (FACT-G)), and safety of zoledronic acid administered every 3-4 weeks to cancer patients with bone metastases with or without skeletal related events.

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

Zoledronic acid in 4 mg starting dose, administered as intravenous infusions for at least 15 minute duration, every 3-4 weeks for a maximum of 6 infusions. Dose adjustments occurred according to creatinine clearance.

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

Not applicable

Criteria for Evaluation

Primary variables

- Pain evaluated on Visual Analogue Scale.
- Time for development of pain summarized for the group, which reported no pain upon study entry.

Secondary variables

- Quality of Life (evaluated by FACT-G questionnaire).
- Time in infusion treatment chair.

Safety and tolerability

- Safety assessment involved monitoring and recording of adverse / serious adverse events, and monitoring of serum creatinine and creatinine clearence values. Adverse events were graded by the investigator, according to Common Toxicity Criteria (CTC) version 3.0. A physical examination within the frame of standard clinical care completes the safety panel.

Pharmacology

Not applicable.

Other:

Not applicable.

Statistical Methods

Sample size for this trial was based on feasibility parameters, not on statistical considerations. Demographic and baseline data were analyzed on the ITT population by a descriptive way. Baseline data were defined as values measured at screening. Safety and tolerability analysis was performed on the safety population. The primary efficacy parameter – pain – was evaluated on the ITT population. Pain scores (VAS scores) are presented both in a descriptive way and analyzed by a statistical test, Repeated Measures ANOVA modeling. The within-subjects main effect was the treatment. Secondary endpoints (FACT-G quality of life index, time in infusion chair) were analyzed on the PP population. Beyond descriptive statistics, changes from baseline in FACT-G total scores and the four sub-scales at infusion two and at final visit were tested by Repeated Measures ANOVA models.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Ambulatory patients at trial entry, aged over 18 years.
- Proof of breast cancer or prostate cancer.
- Breast cancer or prostate cancer in the medical history, proven by biopsy.
- Diagnosis of at least one cancer-related bone lesion with or without SREs that is detectable

on conventional radiographs of bone (plain film) or bone scan at screening.

- Patients with purely lytic, mixed lytic/sclerotic or purely sclerotic bone metastases are eligible.
- Breast cancer patients can be on first, second, or third-line hormonal therapy and on chemotherapy at trial entry.
- Life expectancy exceeding 6 months.
- Negative pregnancy test for patients of childbearing potential.
- ECOG performance status of 0, 1 or 2.

Exclusion Criteria:

- Patients with abnormal renal function as evidenced by either serum creatinine > 1.5 X ULN or calculated creatinine clearance of 60 ml/minute or less.
- Corrected (adjusted for serum albumin) serum calcium concentration < 8.0 mg/dl (2.00 mmol/L).
- Patients with clinically symptomatic brain metastases.
- Known hypersensitivity to zoledronic acid or other bisphosphonates.
- Pregnancy or lactation.
- Women of childbearing potential not on a medically recognized form of contraception.

Number of Subjects

	Zoledronic acid 4 mg/I.V/for every 3-4 weeks
Planned N	Approximately 70
Randomized n	70
Intent-to-treat population (ITT) n (%)	63 (90%)
Completed n (%)	60 (86%)
Withdrawn n (%)	10 (14%)
Withdrawn due to adverse events n (%)	0
Withdrawn due to lack of efficacy n (%)	0
Withdrawn for other reasons n (%)	10 (14%)

Demographic and Background Characteristics

	Zoledronic acid 4 mg/I.V/for every 3-4 weeks.
N (ITT)	63
Females : males	33 (52.4%):30 (47.6%)
Mean age, years (SD)	63.0 (9.7)
Race: White n (%) Black n (%) Other n (%)	63 (100%) 0 0
Diagnosis at screening:	

Breast cancer patient's n (%)	33 (52,4%)
Prostrate cancer patient's n (%)	30 (47,6%)
SRE present n (%)	14 (22,2%)
No SRE present n (%)	49 (77.8%)

Primary Objective Result(s)

Pain: Descriptive statistics by primary cancer

			Record the pain score meas-ured for this pa-tient at this visit! (mm)	Visual analog scale for pain (mm) (visit 1)	Visual analog scale for pain (mm) (visit 2)	Visual analog scale for pain (mm) (visit 3)	Visual analog scale for pain (mm) (visit 4)	Visual analog scale for pain (mm) (visit 5)	Visual analog scale for pain (mm) (visit 6)	Visual analog scale for pain (mm) (End of visit)
Primary cancer diagno-sis	Breast cancer	Mean	43.7	39.1	32.7	28.0	24.9	25.5	20.1	16.0
		Std de-viation	27.4	27.4	27.2	24.0	23.7	19.9	16.6	15.6
		Valid N	N=30	N=30	N=30	N=29	N=29	N=28	N=27	N=29
	Prostrate cancer	Mean	28.7	31.3	33.4	29.6	32.5	26.8	22.2	20.7
		Std de-viation	21.0	24.3	26.3	21.6	26.1	23.3	23.4	24.1
		Valid N	N=27	N=27	N=24	N=23	N=21	N=20	N=19	N=18
Total	Mean		36.3	35.4	33.0	28.7	28.1	26.0	20.9	17.8
	Std deviation		25.4	26.1	26.5	22.8	24.8	21.2	19.5	19.2
	Valid N		N=57	N=57	N=54	N=52	N=50	N=48	N=46	N=47

Change in pain from baseline: Descriptive statistics by primary cancer

			Change of pain from baseline (visit 1)	Change of pain from baseline (visit 2)	Change of pain from baseline (visit 3)	Change of pain from baseline (visit 4)	Change of pain from baseline (visit 5)	Change of pain from baseline (visit 6)	Change of pain from baseline (End of visit)
Primary can-cer diagnosis	Breast cancer	Mean	-3.97	-10.37	-14.79	-17.83	-18.75	-22.89	-25.90
		Std de-viation	11.58	17.47	22.96	25.61	26.26	24.00	26.00
		Valid N	N=30	N=30	N=29	N=29	N=28	N=27	N=29
	Prostrate cancer	Mean	2.56	3.21	-.61	1.67	-2.60	-6.95	-7.00
		Std de-viation	11.56	17.80	16.60	24.31	24.88	25.70	26.22
		Valid N	N=27	N=24	N=23	N=21	N=20	N=19	N=18
Total	Mean		-.88	-4.33	-8.52	-9.64	-12.02	-16.30	-18.66
	Std deviation		11.93	18.73	21.42	26.66	26.67	25.69	27.42
	Valid N		N=57	N=54	N=52	N=50	N=48	N=46	N=47

Pain: Descriptive statistics by skeletal related events

			Record the pain score meas-ured for this pa-tient at this visit! (mm)	Visual analog scale for pain (mm) (visit 1)	Visual analog scale for pain (mm) (visit 2)	Visual analog scale for pain (mm) (visit 3)	Visual analog scale for pain (mm) (visit 4)	Visual analog scale for pain (mm) (visit 5)	Visual analog scale for pain (mm) (visit 6)	Visual analog scale for pain (mm) (End of visit)
Skeletal related events did the patient had any? (SREs like patho-logic bone fractures, spinal cord)	No	Mean	35.1	34.5	32.8	30.0	27.8	26.4	21.1	16.6
		Std de-viation	25.5	27.1	27.3	23.7	25.5	22.1	21.4	18.5
		Valid N	N=44	N=44	N=41	N=40	N=38	N=36	N=34	N=34
	Yes	Mean	40.4	38.6	33.8	24.2	29.2	25.0	20.5	20.8
		Std de-viation	25.7	23.0	24.8	19.7	23.3	19.0	13.2	21.5
		Valid N	N=13	N=13	N=13	N=12	N=12	N=12	N=12	N=13
Total	Mean		36.3	35.4	33.0	28.7	28.1	26.0	20.9	17.8
	Std deviation		25.4	26.1	26.5	22.8	24.8	21.2	19.5	19.2
	Valid N		N=57	N=57	N=54	N=52	N=50	N=48	N=46	N=47

Change in pain from baseline: Descriptive statistics by skeletal related events

			Change of pain from baseline (visit 1)	Change of pain from baseline (visit 2)	Change of pain from baseline (visit 3)	Change of pain from baseline (visit 4)	Change of pain from baseline (visit 5)	Change of pain from baseline (visit 6)	Change of pain from baseline (End of visit)
Skeletal re-lated events did the patient had any? (SREs like pathologic bone frac-tures, spinal cord)	No	Mean	-.61	-3.61	-6.50	-9.45	-11.22	-15.38	-18.32
		Std de-viation	13.28	18.51	21.17	27.06	27.72	26.61	27.21
		Valid N	N=44	N=41	N=40	N=38	N=36	N=34	N=34
	Yes	Mean	-1.77	-6.62	-15.25	-10.25	-14.42	-18.92	-19.54
		Std de-viation	5.61	20.01	21.77	26.48	24.21	23.75	29.07
		Valid N	N=13	N=13	N=12	N=12	N=12	N=12	N=13
Total	Mean		-.88	-4.33	-8.52	-9.64	-12.02	-16.03	-18.66
	Std deviation		11.93	18.73	21.42	26.66	26.67	25.69	27.42
	Valid N		N=57	N=54	N=52	N=50	N=48	N=46	N=47

Secondary Objective Result(s)

FACT-G Total score: Descriptive statistics by primary cancer

			Total score	Total score (visit 2)	Total score (End of visit)
Primary cancer diagnosis	Breast cancer	Mean	51.6	50.5	47.3
		Std deviation	9.0	8.3	8.6
		Valid N	N=33	N=33	N=32
	Prostrate cancer	Mean	50.1	49.6	47.7
		Std deviation	8.0	7.7	9.9
		Valid N	N=27	N=25	N=20
Total	Mean		51.0	50.2	47.4
	Std deviation		8.5	8.0	9.0
	Valid N		N=60	N=58	N=52

FACT-G Total score: Descriptive statistics by skeletal related events

			Total score	Total score (visit 2)	Total score (End of visit)
Skeletal related events did the patient had? (SREs like pathologic bone fractures, spinal cord)	No	Mean	50.9	49.6	47.4
		Std deviation	8.5	8.0	9.0
		Valid N	N=46	N=45	N=49
	Yes	Mean	51.2	52.2	47.4
		Std deviation	9.0	8.1	9.4
		Valid N	N=14	N=13	N=13
Total	Mean		51.0	50.2	47.4
	Std deviation		8.5	8.0	9.0
	Valid N		N=60	N=58	N=52

Time in infusion chair: Descriptive statistics by primary cancer

			Time in infusion chair (visit 3)	Time in infusion chair (visit 5)
Primary cancer diagnosis	Breast cancer	Mean	106.9	112.2
		Std deviation	73.4	66.9
		Median	84	93
		Range	355	295
		Valid N	N=32	N=31
	Prostrate cancer	Mean	175.6	157.0
		Std deviation	121.7	125.4
		Median	120	115
		Range	425	430
		Valid N	N=25	N=22
Total	Mean		137.1	130.8
	Std deviation		102.5	97.1
	Median		95	100
	Range		445	450
	Valid N		N=57	N=53

Time in infusion chair: Descriptive statistics by skeletal related events

			Time in infusion chair (visit 3)	Time in infusion chair (visit 5)
Skeletal related events did the patient had any? (SREs like pathologic bone fractures, spinal cord)	No	Mean	133.5	119.8
		Std deviation	105.8	90.7
		Median	90	90
		Range	445	450
		Valid N	N=45	N=41
	Yes	Mean	150.4	168.6

		Std deviation	92.1	112.3
		Median	113	128
		Range	287	374
		Valid N	N=12	N=12
Total	Mean		137.1	130.8
	Std deviation		102.5	97.1
	Median		95	100
	Range		445	450
	Valid N		N=57	N=53

Safety Results

Summary of safety: No patients died during the study. Eighteen patients (25.7% of safety population) experienced 27 AEs and twelve of them were SAEs. The rate and number (26,3% and 25%, or 10 and 8 patients, for breast cancer and prostate cancer, respectively) of adverse events was similar in both groups defined by primary cancer. The majority of AEs were of lower CTC grades 1 or 2 (20 of 24 events). The remaining 4 events of higher severity CTC grades comprised of hypoglycemia (Grade 3), hyperglycemia (Grade 3), pseudo membranous colitis (Grade 3), and bowel obstruction (Grade 4).

None of the non-serious AEs or SAEs were suspected to be in relationship to the study.

10 most frequently reported adverse events, by preferred term n (%) in safety population

	Zoledronic acid 4 mg/I.V/for every 3-4 weeks.
No of patients with AE(s)	18 (25.7)
Anemia	5 (7.1)
Leucopenia	3 (4.3)
Pain	3 (4.3)
Bowel obstruction	1 (1.4)
Dysuria	1 (1.4)
Hyperglycemia	1 (1.4)
Hypoglycemia	1 (1.4)
Pancreatitis	1 (1.4)
Pneumonia	1 (1.4)
Pseudomembranous colitis	1 (1.4)

SAE, other significant events, and deaths in safety population

	Zoledronic acid 4 mg/I.V/for every 3-4 weeks N=70
	n (%)
Deaths	0

SAEs	12 SAEs, including 4 anaemia 1 hypoglycaemia 1 pseudomembranous colitis 1 bowel obstruction 1 dysuria 1 agranulocytosis 1 hyperglycaemia 1 pancreatitis 1 pneumonia
Discontinued due to SAEs	0

Other Relevant Findings

None

Date of Clinical Trial Report

05 June 2009

Date Inclusion on Novartis Clinical Trial Results Database

21 October 2009

Date of Latest Update