Full Novartis CTRD Results Template

Sponsor

Novartis

Generic Drug Name

zoledronic acid

Therapeutic Area of Trial

Osteoporosis

Approved Indication

Non-oncology indications include the treatment of Paget's disease of the bone, treatment of osteoporosis in postmenopausal women, treatment of osteoporosis in men, prevention and treatment of glucocorticoid-induced osteoporosis, prevention of postmenopausal osteoporosis and prevention of clinical fractures after hip fracture in men and women. In addition, zoledronic acid is indicated for the treatment of hypercalcemia of malignancy and for the prevention, reduction, and/or delay of skeletal muscle related events in cancer patients with solid tumor and bone metastases, or multiple myeloma with bone lesions (marketed as Zometa®).

Protocol Number

CZOL446M2309

Title

A two year multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the fracture efficacy and safety of intravenous zoledronic acid 5 mg annually for the treatment of osteoporosis in men

Phase of Development

Phase III

Study Start/End Dates

08-Dec-2006 to 14-Oct 2010

Study Design/Methodology

This is a two year multi-centered, randomized, double-blind, placebo controlled, parallel group study in male patients with osteoporosis. Patients were randomized in a 1:1 ratio to receive zoledronic acid 5 mg i.v. or placebo i.v. annually. Additionally, all patients were to take a minimum of 1000-1500 mg calcium and 800-1200 IU Vitamin D per day beginning at Visit 1.

Centres

Patients were randomized in a total 134 centers in 23 countries: Argentina (8), Australia (2), Austria (2), Belgium (12), Brazil (5), Czech Republic (6), Denmark (5), Finland (3),Germany (14), Hungary (5), Iceland (1), Italy (3), Norway (7), Poland (2), Portugal (2), Romania (4),Russia (9), Slovakia (6), South Africa (3), Spain (11), Sweden (9), Switzerland (8), and United Kingdom (7)

Publication

None

Objectives

Primary objective(s)

- The number of new morphometric vertebral fractures over 24 months

Secondary objective(s)

- Time to first clinical vertebral fracture
- Proportion of patients with at least one new morphometric vertebral fracture over 12 months.
- Proportion of patients with at least one new moderate or severe morphometric vertebral fracture over 12 and 24 months
- Change in height at Month 12 and Month 24.
- Percent change of BMD (bone mineral density) at lumbar spine and total hip at Month 6, Month 12 and Month 24 relative to baseline as measured by DXA in a sub-set of at least 100 evaluable patients at selected sites.

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

Zoledronic Acid
5 mg/100 ml, i.v. infusion once annually

Placebo
100 ml, i.v. infusion once annually

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

Not applicable

Criteria for Evaluation

Primary variables

- New morphometric vertebral fractures as determined by decrease in percent of vertebral height.

Secondary variables

- Time to first clinical vertebral fracture
- Proportion of patients with at least one new morphometric vertebral fracture over 12 months.
- Proportion of patients with at least one new moderate or severe morphometric vertebral fracture over 12 and 24 months
- Change in height at Month 12 and Month 24 relative to baseline
- Percent change in BMD at lumbar spine and total hip at Months 6, 12, and 24 relative to baseline as measured by DXA in a sub-set of at least 100 evaluable patients at selected sites

Safety and tolerability

Safety assessments consisted of monitoring and recording all AEs and serious adverse events (SAEs), the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and body weight, and the performance of physical examinations. Other safety assessments included special renal safety monitoring, bone safety monitoring, and adjudication of targeted safety information (maxillofacial complications including osteonecrosis of the jaw (ONJ) and arrhythmia serious adverse events).

The overall percentage of AEs was higher for zoledronic acid (90.8%) compared with placebo (76.3%). The most frequently affected PSOCs (i.e., ≥ 25.0% for any treatment group) were the following: musculoskeletal and connective tissue disorders; general disorders and administration site conditions; infections and infestations; and nervous system disorders. Many of the common AEs seen in the zoledronic acid group are associated with post-dose symptoms observed with i.v. and high dose oral bisphosphonates.

The majority of patients reported AEs (90.8% in the zoledronic acid group and 76.3% in the placebo group).

- Post-dose symptom AEs (e.g., myalgia, pyrexia, headache, arthralgia, chills, fatigue) occurred more commonly in the zoledronic acid group within 3 days of study drug administration. The majority of these AEs resolved within 3 days of onset.
- Overall mortality rate was similar for the two treatment groups (2.6% zoledronic acid vs. 2.9% placebo).
- SAEs occurred in a similar percentage of patients (25.3% zoledronic acid vs. 25.2% placebo).

• Discontinuations from study drug occurred in a similar percentage of patients (3.9% zoledronic acid vs. 3.8% placebo).

Pharmacology

N/A

Other

• There was no evidence of an increased risk of cardiac-related death, arrhythmia SAEs, ONJ, or long-term renal dysfunction with zoledronic acid.

Evaluation of various potential indicators of renal dysfunction included the following:
• Occurrence of renal abnormalities defined as a(n) 1) increase from baseline in serum creatinine of more than 0.5 mg/dL, 2) protein urinary dipstick >2+, 3) calculated creatinine clearance < 30 mL/min, or 4) decrease from baseline in creatinine clearance of ≥30% when baseline was ≤ 60 mL/min
• Occurrence of AEs associated with a change in renal function

The occurrence of renal abnormalities, as defined in the first category above, overall during the study was lower in the zoledronic acid group compared with the placebo group. This was also seen for the second category of events: 12 (2.0%) of patients in the zoledronic acid group and 21 (3.4%) of patients in the placebo group had AEs associated with a change in renal function .

Statistical Methods

The primary efficacy endpoint was the proportion of subjects with at least one new morphometric vertebral fracture over 24 months. The primary efficacy analysis was based on a logistic regression model with treatment, number of baseline vertebral fractures, and region as explanatory variables to assess the between-treatment difference in the proportion of subjects with new morphometric vertebral fracture over 24 months in the modified intent-to-treat (mITT) population. Missing fracture outcome status at Month 24 was imputed using Month 12 x-ray (LOCF method).

Between-treatment differences in the proportion of subjects with new, moderate or severe, and new or worsening morphometric vertebral fracture over a time period for secondary objectives were performed similarly to the primary analysis. Between-treatment differences in clinical fractures were evaluated using a Cox regression model with treatment as factor on the ITT population. Between-treatment comparison of change from baseline in stadiometer height was evaluated on the ITT population using an analysis of covariance (ANCOVA) model with treatment, baseline height and region as explanatory variables. The analysis of each secondary objective related to BMD was performed using an ANCOVA model with treatment and baseline value as explanatory variables in the ITT population.
The analysis of biomarkers at each time point was carried out using an ANCOVA model with treatment and log baseline value as explanatory variables. The analysis variable was the ratio of the post-baseline value relative to baseline (relative change) using loge transformation.

No interim analysis was performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- male patients between 50 and 85 years of age
- Bone mineral density T-score of less than or equal to -2.5 SD at the total hip or femoral neck OR less than or equal to -2.5 SD at the lumbar spine as confirmed by the central expert reader.

Or

- Bone mineral density T-score of less than or equal to -1.5 SD at the total hip or femoral neck as confirmed by the central expert reader, AND at least 1 up to a maximum of 3 prevalent vertebral fractures of mild or moderate grade as defined by the modified Genant method for males and confirmed by the central expert reader. As per Amendment 2, this inclusion criterion is not applicable in Finland.

Exclusion criteria

- Patients with 25-(OH) Vitamin D levels less than 15 ng/mL at Visit 1. If the vitamin D level is < 15 ng/ml the patient should receive a loading dose of 75,000-100,000 IU of vitamin D IM or orally once at visit 1 and have the vitamin D test repeated at visit 1A (to be done after at least 3 weeks have passed).
- Baseline renal insufficiency (calculated creatinine clearance less than 30.0 mL/min) at Visit 1 and/or Visit 1A
- Serum calcium less than or equal to 2.0 mmol/L (8.0 mg/dL) at Visit 1 or Visit 1A
- AST or ALT greater than three times the upper limit of normal
- Serum alkaline phosphatase greater than 1.5 times the upper limit of normal

For those patients qualifying via BMD at the lumbar spine and/or belonging to the subset of at least 100 patients at the selected sites, any disease or deformation of the spine that would preclude the proper acquisition of a lumbar spine DXA (L1-L4) e.g., implantable devices, scoliosis, ankylosing spondylitis.

Number of Subjects

	Novartis product	**Placebo**
Planned N	536	536
Randomised n	588	611
Intent-to-treat population (ITT) n (%)	588 (100%)	611 (100%)
Completed n (%)	530 (90.1%)	540 (88.4%)
Withdrawn n (%)	58 (9.9%)	71(11.6%)
Withdrawn due to adverse events n (%)	26 (4.4%)	29 (4.7%)
Withdrawn due to lack of efficacy n (%)	0	4 (0.7%)
Withdrawn for other reasons n (%)	32 (5.4%)	38 (6.2%)

Demographic and Background Characteristics

	Novartis product	Comparator
N (ITT)	588	611
Males (only)	588	611
Mean age, years (SD)	65.8 (8.3)	65.7 (8.6)
Mean weight, kg (SD)	74.1 (12.4)	73.9 (13.1)
Race White n (%) Black n (%) Asian n (%) Other n (%)	 555 (94.4) 5 (0.9) 2 (0.3) 26 (4.4)	 578 (94.6) 3 (0.5) 0 30 (4.9)
Characteristics relevant to study population (eg, mean FEV1 % predicted [SD])	N/A	N/A

Primary Objective Result(s)

Between-treatment comparison of the proportion of patients with at least one new morphometric vertebral fracture over 24 months (mITT population)

Zoledronic acid n/N (%)	Placebo n/N (%)	Relative risk (95% CI)	Odds ratio (95% CI)	p-value
9/553 (1.6)	28/574 (4.9)	0.33 (0.16, 0.70)	0.32 (0.14, 0.66)	0.0016

- N = the number of subjects in the analysis population.
- n = the number of subjects with the event. (%)= n/N*100.
- CI = confidence interval.
- The relative risk is calculated based on a 2x2 table and the normal approximation is used to calculate its 95% CI. A relative risk < 1 implies that the likelihood of having the event is less in zoledronic acid than in placebo.
- The odds ratio, its 95% CI, and p-value are calculated from a logistic regression with treatment, region, and number of baseline vertebral fractures (0, 1, ≥2) as covariates using the log-likelihood type approach. An odds ratio < 1 implies that the odds of having the event is less in zoledronic acid than in placebo.

Secondary Objective Result(s)

Between-treatment comparison of secondary efficacy endpoints (mITT population)

Endpoint	Zoledronic acid n/N (%)	Placebo n/N (%)	Relative risk (95% CI)	Odds ratio (95% CI)	p-value
At least one new morphometric vertebral fracture over 12 months	5/553 (0.9)	16/574 (2.8)	0.32 (0.12, 0.88)	0.32 (0.10, 0.82)	0.0166
At least one new moderate or severe morphometric vertebral fracture over 12 months	2/553 (0.4)	11/574 (1.9)	0.19 (0.04, 0.85)	0.19 (0.03, 0.71)	0.0117
At least one new moderate or severe morphometric vertebral fracture over 24 months	6/553 (1.1)	17/574 (3.0)	0.37 (0.15, 0.92)	0.37 (0.13, 0.89)	0.0260
At least one new or worsening morphometric vertebral fracture over 12 months	7/553 (1.3)	16/574 (2.8)	0.45 (0.19, 1.10)	0.45 (0.17, 1.06)	0.0677
At least one new or worsening morphometric vertebral fracture over 24 months	11/553 (2.0)	28/574 (4.9)	0.41 (0.21, 0.81)	0.39 (0.18, 0.77)	0.0065

- N = the number of patients in the analysis population.
- n = the number of patients with the event. (%)=n/N*100.
- CI = confidence interval
- The relative risk is calculated based on a 2x2 table and the normal approximation is used to calculate its 95% CI. A relative risk < 1 implies that the likelihood of having the event is less in zoledronic acid than in placebo.
- The odds ratio, its 95% CI, and p-value are calculated from a logistic regression with treatment, region, and number of baseline vertebral fractures (0, 1, >=2) as covariates using the log-likelihood type approach. An odds ratio < 1 implies that the odds of having the event is less in zoledronic acid than in placebo.
- For the endpoints at 24 months, the LOCF method is used to impute any missing values at Month 24.

Between-treatment comparison of percentage change from baseline in lumbar spine BMD (g/cm^2), total hip BMD (g/cm^2) and femoral neck BMD (g/cm^2), by visit (ITT population)

BMD Site	Visit	Treatment	n	LSM (SE)	Treatment difference (95% CI)	p-value
Lumbar spine	Month 6	Zoledronic acid	61	4.87 (0.412)	4.77 (3.62,5.93)	<0.0001
		Placebo	61	0.10 (0.412)		
	Month 12	Zoledronic acid	60	5.51 (0.437)	4.67 (3.45,5.88)	<0.0001
		Placebo	62	0.84 (0.430)		
	Month 24	Zoledronic acid	58	7.73 (0.459)	6.12 (4.85,7.39)	<0.0001
		Placebo	61	1.61 (0.448)		
Total hip	Month 6	Zoledronic acid	60	1.38 (0.294)	1.82 (1.00,2.63)	<0.0001
		Placebo	63	-0.44 (0.287)		
	Month 12	Zoledronic acid	58	1.66 (0.283)	1.40 (0.62,2.17)	0.0005
		Placebo	64	0.26 (0.269)		
	Month 24	Zoledronic acid	56	2.31 (0.346)	2.15 (1.21,3.09)	<0.0001
		Placebo	63	0.16 (0.326)		
Femoral neck	Month 6	Zoledronic acid	60	2.21 (0.448)	1.63 (0.39,2.87)	0.0103
		Placebo	63	0.58 (0.437)		
	Month 12	Zoledronic acid	58	2.06 (0.465)	1.47 (0.20,2.74)	0.0241
		Placebo	64	0.59 (0.443)		
	Month 24	Zoledronic acid	56	3.39 (0.544)	3.30 (1.82,4.78)	<0.0001
		Placebo	63	0.09 (0.513)		

- BMD was evaluated centrally in a predefined subset of subjects in selected sites.
- Percentage change from baseline = 100*(endpoint - baseline)/baseline).
- n = the number of subjects with evaluable measurements at both baseline and the post-baseline visit, as determined by the efficacy window.
- LSM = least squares mean, SE = standard error of LSM, CI = confidence interval.
- Treatment difference = the LSM difference of zoledronic acid vs. placebo in the percent change from baseline.
- LSM for each treatment group, treatment difference and the p-value are obtained from an ANCOVA on the percent change from baseline with treatment and baseline BMD as explanatory variables.
- * = Measurements were performed in a predefined subset of subjects in selected sites.

Safety Results

Adverse events, overall and by primary system organ class and treatment group (Safety population)

Primary system organ class	Zoledronic acid N=588 n (%)	Placebo N=611 n (%)
-Any primary system organ class	534 (90.8)	466 (76.3)
Musculoskeletal and connective tissue disorders	340 (57.8)	231 (37.8)
General disorders and administration site conditions	243 (41.3)	92 (15.1)
Infections and infestations	186 (31.6)	201 (32.9)
Nervous system disorders	152 (25.9)	99 (16.2)
Gastrointestinal disorders	142 (24.1)	139 (22.7)
Injury, poisoning and procedural complications	89 (15.1)	94 (15.4)
Vascular disorders	85 (14.5)	81 (13.3)
Respiratory, thoracic and mediastinal disorders	64 (10.9)	62 (10.1)
Metabolism and nutrition disorders	60 (10.2)	59 (9.7)
Cardiac disorders	54 (9.2)	48 (7.9)
Renal and urinary disorders	46 (7.8)	48 (7.9)
Skin and subcutaneous tissue disorders	46 (7.8)	39 (6.4)
Eye disorders	41 (7.0)	28 (4.6)
Psychiatric disorders	41 (7.0)	36 (5.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	38 (6.5)	37 (6.1)
Investigations	34 (5.8)	39 (6.4)
Reproductive system and breast disorders	27 (4.6)	25 (4.1)
Ear and labyrinth disorders	22 (3.7)	27 (4.4)
Blood and lymphatic system disorders	18 (3.1)	20 (3.3)
Hepatobiliary disorders	12 (2.0)	14 (2.3)
Endocrine disorders	8 (1.4)	7 (1.1)
Immune system disorders	4 (0.7)	5 (0.8)
Social circumstances	3 (0.5)	1 (0.2)
Congenital, familial and genetic disorders	2 (0.3)	3 (0.5)

- N = the number of patients in the analysis population.
- n = the number of patients with the event. (%)= 100*n/N.
- A patient with multiple adverse events is counted only once in the any primary system organ class row.
- A patient with multiple adverse events within a primary system organ class is counted only once.
- Primary system organ classes are presented by descending frequency of the zoledronic acid group.

Most frequent adverse events (at least 5% in any group) and by preferred term and treatment group (Safety population)

Preferred term	Zoledronic acid N=588 n (%)	Placebo N=611 n (%)
-Any preferred term	534 (90.8)	466 (76.3)
Pyrexia	143 (24.3)	23 (3.8)
Myalgia	129 (21.9)	25 (4.1)
Arthralgia	123 (20.9)	68 (11.1)
Back pain	84 (14.3)	74 (12.1)
Headache	82 (13.9)	27 (4.4)
Hypertension	50 (8.5)	46 (7.5)
Nasopharyngitis	50 (8.5)	49 (8.0)
Pain in extremity	44 (7.5)	23 (3.8)
Chills	40 (6.8)	5 (0.8)
Fatigue	40 (6.8)	13 (2.1)
Influenza	30 (5.1)	28 (4.6)
Influenza like illness	30 (5.1)	14 (2.3)
Musculoskeletal pain	30 (5.1)	19 (3.1)
Osteoarthritis	30 (5.1)	12 (2.0)
Traumatic fracture	28 (4.8)	36 (5.9)
Fall	23 (3.9)	31 (5.1)

- N = the number of patients in the analysis population.
- n = the number of patients with the event. (%)= 100*n/N.
- A patient with multiple adverse multiple occurrences of an AE within a preferred term is counted only once.
- Preferred terms are sorted by descending order of incidence in the zoledronic acid group.

Patients who died, had other serious or clinically significant adverse events or discontinued due to adverse events or lab abnormalities, by treatment group (Safety population)

	Zoledronic acid N=588 n (%)	Placebo N=611 n (%)
Total no. of patients with serious or significant AEs	158 (26.9)	162 (26.5)
Deaths	15 (2.6)	18 (2.9)
SAEs	149 (25.3)	154 (25.2)
AE causing discontinuation of study drug	23 (3.9)	23 (3.8)
SAEs causing discontinuation of study drug	13 (2.2)	11 (1.8)
Non-serious AEs causing discontinuation of study drug	11 (1.9)	12 (2.0)
AEs causing discontinuation from study	11 (1.9)	11 (1.8)
Lab abnormalities causing discontinuation from study	0	0

- N = the number of patients in the analysis population
- n = the number of patients with the event. (%)= 100*n/N

Serious Adverse Events and Deaths

Renal laboratory values and changes meeting pre-specified criteria during the study, by treatment group (Safety population)

	Zoledronic acid N=588		Placebo N=611	
	Total	n (%)	Total	n (%)
Increase in serum creatinine > 0.5 mg/dL	584	14 (2.4)	610	18 (3.0)
Urinary protein - dipstick > 2+	556	1 (0.2)	572	1 (0.2)
Treatment emergent creatinine clearance < 30 mL/min	557	3 (0.5)	577	9 (1.6)
Baseline creatinine clearance ≤ 60 mL/min and decreased at least 30%	90	6 (6.7)	112	10 (8.9)

- N = the number of subjects in the analysis population.
- Total = the number of subjects with evaluable measurements at both baseline and the post-baseline visit as determined by the analysis window.
- n = the number of subjects meeting the criterion. - (%)= 100*n/Total.
- For the criterion of protein urine dipstick, only subjects with a baseline urine dipstick <= 2+ are included.
- For the criterion of creatinine clearance < 30 mL/min, only subjects with a baseline creatinine clearance >= 30 mL/min are included.
- For the criterion of baseline creatinine clearance <= 60 mL/min and decreased at least 30%, only subjects with a baseline creatinine clearance <= 60 mL/min are included.

Serum creatinine levels for patients with >0.5 mg/dL increase from baseline or pre-dose at Days 9-11 after the 1st or 2nd infusion

		Serum creatinine (mg/dL)						
		V2	V3	V4	V6	V7	V8	V10
Patient ID	Age	BL	Days 9-11 after 1st dose	Month 3	Month 12 (pre-dose)	Days 9-11 after 2nd dose	Month 15	Month 24
Zoledronic acid								
0101-00023	67	1.0	1.1	1.1	1.2	**1.9**	1.4/1.3	1.4
0152-00007	73	1.2	**1.9**	1.5	1.5	1.5	1.6	1.5
0163-00043	85	1.7	1.5	1.6	1.9	**6.5**	2.7	2.4/2.5
0851-00002*	69	1.0	1.3	1.9	1.9/1.7	**1.8**	1.8	2.0/1.8
0205-00131	70	1.1	1.4	1.1	1.1	**1.7**	1.1	1.1
0552-00022	63	1.0	0.9	1.2	1.1	**2.0**	1.0	1.0
0657-00001	69	1.0	**1.8**	0.9/1.0	0.9	1.0	1.1	1.0
0401-00012*	56	1.0	1.0	1.0	1.5/1.4	**1.5**	1.5	NA
Placebo								
0852-00076	76	1.3	1.4	1.3	1.8/1.6	**2.0**	2.0	NA
0106-00002*	63	1.0	1.1	1.0	1.7/2.1	**2.0**	1.9	NA

BL=baseline; V=visit; NA=not available
Note: When two values are present for any given time point, the second one is the re-test value.
*Patient received only the 1st study drug infusion.

There was no evidence of an increased risk of cardiac-related death, arrh
long-term renal dysfunction with zoledronic acid.

Other Relevant Findings

Because biphosphonates are excreted by the kidney and are known to have the potential
when given i.v. and administered as a bolus, particular attention was paid to renal safet

Evaluation of renal dysfunction included the following:

- Increase from baseline in serum creatine of more than 0.5 mg/dL, protein urine c
  clearance, 30 mL/min, or decrease from baseline in creatine clearance of≥30%w
- Occurrence of AEs associated with renal function.

Adverse events associated with a change in renal function, regardless of study drug relationship, by preferred term and treatment group
Safety population

Preferred term	Zoledronic acid N=588 n (%)	Placebo N=611 n (%)
-Any preferred term		
-Total	12 (2.0)	21 (3.
Renal impairment	3 (0.5)	5 (0.
Blood creatinine increased	2 (0.3)	3 (0.
Renal failure	2 (0.3)	5 (0.
Renal failure acute	2 (0.3)	0
Creatinine renal clearance decreased	1 (0.2)	3 (0.
Proteinuria	1 (0.2)	4 (0.
Renal failure chronic	1 (0.2)	2 (0.

- N = the number of subjects in the analysis population.
- n = the number of subjects with the event.
- (%)= 100*n/N.
- Preferred terms are sorted in descending frequency, as reported in Zoledronic acid first.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Date of Clinical Trial Report

26-Apr-2011

Date Inclusion on Novartis Clinical Trial Results Database

13-Oct-2011

Date of Latest Update