Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Zoledronic acid

Therapeutic Area of Trial

Osteoporosis in postmenopausal women

Approved Indication

The indications in which usage of zoledronic acid is approved are:

- Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures and to increase bone mineral density
- Prevention of clinical fractures after hip fracture in men and women
- Treatment of osteoporosis in men
- Treatment and prevention of glucocorticoid-induced osteoporosis
- Prevention of postmenopausal osteoporosis
- Treatment of Paget's disease of bone

Study Number

CZOL446H2409

Title

A one-year partial double-blinded, randomized, multi-center, multi-national study to assess the effects of combination therapy of annual zoledronic acid (5 mg) and daily subcutaneous teriparatide (20 µg) on postmenopausal women with osteoporosis

Phase of Development

IIIB / IV

Study Start/End Dates

04-Dec-2006 (first patient screened), 03-Feb-2009 (last patient completed)

Study Design/Methodology

This was a 1-year partial double-blinded, randomized, multicenter, multinational study to assess the effects of combination once-yearly zoledronic acid plus daily subcutaneous teriparatide administered concurrently on postmenopausal women with osteoporosis. A 5-week screening period was used to assess patient eligibility and to determine if the patient had adequate renal func-

tion to participate in the trial. Eligible patients were randomized to one of 3 treatment groups in a 1:1:1 allocation at the baseline visit. The 3 treatment arms were:

1. Zoledronic acid 5 mg i.v. (once at randomization) plus teriparatide 20 µg (daily subcutaneous injections administered concurrently through 52 weeks)

2. Zoledronic acid 5 mg i.v. (once at randomization)

3. Placebo zoledronic acid i.v. (once at randomization) plus teriparatide 20 µg (daily subcutaneous injections administered concurrently through 52 weeks)

It was intended to enroll approximately 360 patients, with 120 patients randomized to each of the three treatment groups.

Centres

A total of 35 centers in 4 countries: Belgium (5), Germany (6), Spain (6), and United States (18).

Publication

None

Objectives

Primary objective(s)

- The primary objective was to demonstrate that combination therapy with once-yearly i.v. zoledronic acid (5 mg) and daily subcutaneous injections of teriparatide (20 µg) is non-inferior to teriparatide treatment alone with respect to percentage increase in lumbar spine bone mineral density (BMD) at 52 weeks. If the non-inferiority was established, the superiority of the combination therapy (zoledronic acid plus teriparatide) over teriparatide treatment alone was to be evaluated.

Secondary objective(s)

The secondary objectives were:

- To evaluate the effect of combination therapy with zoledronic acid (5 mg) and teriparatide (20 µg) compared to teriparatide (20 µg) alone on percent change in total hip BMD at 52 weeks.
- To evaluate the effect of combination therapy with zoledronic acid (5 mg) and teriparatide (20 µg) compared to teriparatide (20 µg) alone on percent change of lumbar spine and total hip BMD at 13 and 26 weeks.
- To evaluate the effect of combination therapy with zoledronic acid (5 mg) and teriparatide (20 µg) compared to zoledronic acid (5 mg) alone on percent change of lumbar spine and total hip BMD at 13, 26, and 52 weeks.
- To evaluate the effect of combination therapy with zoledronic acid (5 mg) and teriparatide (20 µg) compared to teriparatide (20 µg) alone and zoledronic acid (5 mg) alone on serum biochemical markers (P1NP and beta-CTx) at 4, 8, 26, 39 and 52 weeks.

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

- Zoledronic acid 5.0 mg in a ready-to-infuse plastic bottle with a total fill volume of 103 mL to allow an infusion of 100 mL total volume corresponding to 5 mg of zoledronic acid
- Zoledronic acid matched placebo as a 103 mL solution of sterile water (physiologic 0.9% normal saline) to allow an infusion of 100 mL total volume in a ready-to-infuse plastic bottle

Zoledronic acid 5.0 mg/100 mL or placebo 100 mL was administered via a peripheral intravenous site at Visit 2 as a slow 15-minute infusion.

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

Commercially purchased teriparatide (rDNA origin) manufactured by Eli Lilly and Company, as a pre-filled delivery device (pen). Each pen contained a 28-day supply of teriparatide with a dose setting indication that delivered the prescribed 20 µg dose. Teriparatide 20 µg dose was administered concurrently as daily subcutaneous injections for 52 weeks.

Criteria for Evaluation

Primary variables

- The primary efficacy variable was the percent change from baseline in lumbar spine BMD at 52 weeks.

Secondary variables

The secondary efficacy variables were as follows:

- The percentage change in lumbar spine BMD at Weeks 13 and 26 relative to baseline
- The percentage change in total hip BMD at Weeks 13, 26, and 52 relative to baseline
- The relative (to baseline) change in serum bone formation marker P1NP at 4, 8, 26, 39 and Week 52
- The relative (to baseline) change in serum bone resorption marker beta-CTx at 4, 8, 26, 39 and Week 52

Safety and tolerability

- All randomized patients who received study drug were included in the safety evaluation. Safety assessments consisted of monitoring and recording all non-serious and serious adverse events during each contact, the regular monitoring of serum chemistry and urine, and the performance of physical examinations and body weight measurements. Renal safety, bone safety, and clinical fracture events were monitored closely throughout the trial.
- Treatment-emergent adverse events were to be summarized by treatment group.

Pharmacology

NA

Other

NA

Statistical Methods

The primary analysis was based on a 2-sided 95% confidence interval (CI) in the difference of percent change from Baseline at Week 52 in BMD of the lumbar spine (ZOL+PTH minus PTH alone). The CI was calculated using contrast from an analysis of variance model with country and treatment (all three treatments) in the model. The non-inferiority was tested by using the lower

bound of the CI with the predefined non-inferiority margin of -2.0% in ITT and PP populations. The superiority of the combined group (ZOL+PTH) to PTH alone was tested using the contrast from the two-way analysis of variance model, if non-inferiority was established.

The analysis of each secondary objective related to BMD was performed using an analysis of variance model with country and treatment in the model.

The analysis of biomarkers at each time point was carried out using the analysis of covariance model with treatment and country as factors and the baseline biomarker value as a covariate. The analysis was based on the ratio of the post-baseline value relative to baseline (relative change) using a $\log_e$ transformation.

No interim analysis was performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

Females, between 45 and 89 years of age, and postmenopausal with either one of the following:

- BMD T-score of -2.5 or less at femoral neck, total hip or lumbar spine
- BMD T-score of -2.0 or less at femoral neck, total hip or lumbar spine with at least one documented osteoporotic vertebral fracture or a previously documented history of an osteoporotic clinical non-vertebral fracture not due to excessive trauma

Relevant Exclusion criteria

Patients who met the following criteria were excluded:

- Any prior use of strontium ranelate.
- Calculated creatinine clearance <30 mL/min or urine dipstick greater than or equal to 2+ protein at Visit 2 without evidence of contamination or bacteriuria (may be repeated one time at least a week apart if there was suspicion of contamination).
- Prior treatment with oral or i.v. bisphosphonates longer than 3 months consecutively. If bisphosphonate exposure was less than or equal to 3 months, a washout period of 1 year prior to randomization was required.
- Serum calcium ≥ 2.75 mmol/L or ≤ 2.0 mmol/L, 25(OH) vitamin D levels less than 15 ng/mL prior to randomization.
- AST or ALT greater than 3 times the upper limit of normal, serum alkaline phosphatase greater than 1.5 times the upper limit of normal.
- Non-osteoporotic forms of metabolic bone disease such as and not limited to Paget's disease of bone, osteomalacia, osteogenesis imperfecta or multiple myeloma.
- Less than 3 evaluable lumbar (L1-L4) vertebrae, any disease of the spine that would preclude the proper acquisition of a lumbar spine DXA (L1-L4), e.g., implantable devices, scoliosis, ankylosing spondylitis.
- Any disease affecting bone and mineral metabolism (other than osteoporosis).
- Nephrolithiasis or urolithiasis within the previous 2 years.
- Malabsorption.

- Uncorrected abnormal thyroid or parathyroid function, removal of parathyroid or thyroid gland.
- Chronic use of systemic corticosteroids (oral or i.v.) within one year of screening, where the total dose exceeded 750 mg of oral prednisone or equivalent. Note: Use of corticosteroids in forms such as topical creams, nasal or inhaled formulations or those injected locally (intra-articular) were not exclusionary.
- Treatment with selective estrogen receptor modulator (SERMs, i.e., raloxifene), calcitonin or hormone replacement therapy within 3 months of randomization, allergy or previous exposure to teriparatide, previous exposure to exogenous PTH or PTH analogs, previous external beam radiotherapy or implant-radiotherapy of the skeleton, treatment with a investigational drug within the previous 30 days from randomization or history of allergic reaction or sensitivity to bisphosphonates.
- Patients with an active dental infection, unhealed dental extraction or planned oral surgery within 3 months after randomization, history of iritis, uveitis or chronic conjunctivitis.
- Patients meeting the DSM-IV criteria for alcohol/substance abuse and dependence, any medical or psychiatric condition which, in the opinion of the investigator, would preclude the participant from adhering to the protocol or completing the trial per protocol or patients who have trouble injecting themselves and do not have someone who can help them.
- Any of the following cancer exclusions:
  - New diagnosis or active treatment of any malignancy less than or equal to 12 months prior to Visit 1.
  - Evidence/history of any metastases on or prior to randomization.
  - Evidence of paraneoplastic syndrome, especially those characterized by hypercalcemia during screening or by history. Note: Patients with the following could be included: basal cell or squamous carcinoma of the skin, colonic polyps with non-invasive malignancy which have been removed, and carcinoma in situ (CIS) of the breast, cervix or uterus that had been surgically removed.
- Previous major solid organ or bone marrow transplant or on a transplant waiting list.

Number of Subjects

Patient disposition, by treatment (ITT population)

Disposition	Zol 5 mg N=137 n (%)	Zol 5 mg + PTH 20 µg N=137 n (%)	Placebo + PTH 20 µg N=138 n (%)	Total N=412 n (%)
Completed	131 (95.6)	126 (92.0)	131 (94.9)	388 (94.2)
Discontinued	6 (4.4)	11 (8.0)	7 (5.1)	24 (5.8)
Adverse event (s)	2 (1.5)	5 (3.6)	3 (2.2)	10 (2.4)
Subject withdrew consent	1 (0.7)	3 (2.2)	2 (1.4)	6 (1.5)
Lost to follow-up	1 (0.7)	2 (1.5)	2 (1.4)	5 (1.2)
Death	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)
Protocol deviation	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)
Administrative problems	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)

Demographic and Background Characteristics

Demographics, by treatment (ITT population)

Demographic variable	Zol 5 mg N=137	Zol 5 mg + PTH 20 µg N=137	Placebo + PTH 20 µg N=138	Total N=412
Race – n (%)				
Caucasian	135 (98.5)	132 (96.4)	135 (97.8)	402 (97.6)
Other	2 (1.5)	5 (3.6)	3 (2.2)	10 (2.4)
Age (years)				
n	137	137	138	412
Mean	66.1	65.0	63.8	65.0
SD	9.02	8.78	9.08	8.99
Median	67.0	64.0	62.5	65.0
Min	45.0	46.0	45.0	45.0
Max	83.0	86.0	87.0	87.0
Age group (years) – n (%)				
45–64 years	57 (41.6)	69 (50.4)	77 (55.8)	203 (49.3)
65–74 years	50 (36.5)	44 (32.1)	43 (31.2)	137 (33.3)
≥ 75 years	30 (21.9)	24 (17.5)	18 (13.0)	72 (17.5)
Weight (kg)				
n	137	137	138	412
Mean	62.6	63.5	63.6	63.2
SD	12.00	11.11	9.97	11.04
Median	62.0	61.4	61.3	61.8
Min	30.9	40.2	46.8	30.9
Max	110.0	93.2	100.9	110.0

Height (cm)				
n	137	137	138	412
Mean	157.1	158.4	158.7	158.1
SD	7.19	6.96	6.25	6.83
Median	157.0	158.5	158.4	158.2
Min	140.0	141.6	144.0	140.0
Max	172.7	175.3	174.0	175.3
Body mass index (kg/m2)				
n	137	137	138	412
Mean	25.3	25.3	25.3	25.3
SD	4.42	4.14	4.15	4.22
Median	25.0	24.5	24.7	24.6
Min	13.1	17.2	17.7	13.1
Max	41.6	38.0	39.1	41.6

Baseline BMD, by treatment (ITT population)

Baseline variable	Zol 5 mg N=137	Zol 5 mg + PTH 20 µg N=137	Placebo + PTH 20 µg N=138	Total N=412
Standardized lumbar spine BMD (g/cm2)				
n	135	137	138	410
Mean	0.72	0.74	0.73	0.73
SD	0.095	0.096	0.087	0.093
Median	0.72	0.73	0.73	0.73
Min	0.51	0.41	0.54	0.41
Max	1.11	1.11	1.14	1.14
Standardized total hip BMD (g/cm2)				
n	136	137	138	411
Mean	0.68	0.71	0.71	0.70
SD	0.087	0.104	0.087	0.094
Median	0.68	0.71	0.71	0.70
Min	0.46	0.42	0.47	0.42
Max	0.90	1.00	0.94	1.00
Standardized femoral neck BMD (g/cm2)				
n	136	137	138	411
Mean	0.59	0.63	0.63	0.62
SD	0.079	0.094	0.077	0.085
Median	0.58	0.63	0.62	0.61
Min	0.41	0.38	0.42	0.38
Max	0.86	0.94	0.83	0.94
Lumbar spine T-score – n (%)				
≤ -3.0	66 (48.2)	55 (40.1)	59 (42.8)	180 (43.7)
> -3.0 – -2.5	33 (24.1)	47 (34.3)	47 (34.1)	127 (30.8)
> -2.5 – -2.0	17 (12.4)	19 (13.9)	22 (15.9)	58 (14.1)
> -2.0 (1)	18 (13.1)	15 (10.9)	10 (7.2)	43 (10.4)
Missing	3 (2.2)	1 (0.7)	0 (0.0)	4 (1.0)
Lumbar spine T-score				

n	134	136	138	408
Mean	-2.88	-2.79	-2.87	-2.85
SD	0.883	0.892	0.807	0.860
Median	-2.97	-2.80	-2.80	-2.89
Min	-5.05	-6.00	-4.90	-6.00
Max	0.73	0.70	1.10	1.10
Femoral neck T-score				
n	136	137	138	411
Mean	-2.36	-1.98	-2.05	-2.13
SD	0.701	0.817	0.687	0.755
Median	-2.49	-2.05	-2.10	-2.20
Min	-3.90	-4.20	-3.64	-4.20
Max	0.00	0.80	0.08	0.80
Total hip T-score				
n	136	137	138	411
Mean	-2.03	-1.79	-1.79	-1.87
SD	0.726	0.851	0.684	0.763
Median	-2.10	-1.80	-1.73	-1.90
Min	-3.80	-4.50	-3.68	-4.50
Max	-0.40	0.40	0.00	0.40

Primary Objective Result(s)

Between-treatment comparison for percent change in lumbar spine BMD at Week 52 (excluding missing values) relative to baseline (ITT population)

Treatment	n	LSM (SE)	Pair-wise treatment comparison	LSM difference	95% CI of LSM difference (1)	p-value (2)
ZOL 5 mg + PTH 20 µg	122	7.51 (0.414)	(ZOL 5 mg + PTH 20 µg) – (Placebo + PTH 20 µg)	0.46 (0.565)	-0.65, 1.57	0.4147
			(ZOL 5 mg + PTH 20 µg) – (ZOL 5 mg)	3.14 (0.568)	2.02, 4.25	<0.0001
Placebo + PTH 20 µg	131	7.05 (0.398)	(Placebo + PTH 20 µg) – (ZOL 5 mg)	2.68 (0.557)	1.58, 3.77	<0.0001
ZOL 5 mg	128	4.37 (0.401)				

ZOL=zoledronic acid; PTH=parathyroid hormone; SE=standard error; LSM = least squares mean, CI = confidence interval

(1) 95% confidence interval is calculated based on a t-distribution.

(2) p-value is obtained from ANOVA with treatment and country as explanatory variables.

Secondary Objective Result(s)

Between-treatment comparison for percent change in lumbar spine BMD (excluding missing values) relative to baseline, by visit (ITT population)

Treatment	n	LSM (SE)	Pair-wise treatment comparison	LSM difference	95% CI of LSM difference (1)	p-value (2)
Week 13						
ZOL 5 mg + PTH 20 µg	127	4.65 (0.302)	(ZOL 5 mg + PTH 20 µg) – (Placebo + PTH 20 µg)	1.77 (0.418)	0.95, 2.59	<0.0001
			(ZOL 5 mg + PTH 20 µg) – (ZOL 5 mg)	1.68 (0.418)	0.86, 2.50	<0.0001
Placebo + PTH 20 µg	131	2.88 (0.297)	(Placebo + PTH 20 µg) – (ZOL 5 mg)	-0.09 (0.415)	-0.91, 0.72	0.8249
ZOL 5 mg	131	2.97 (0.297)				
Week 26						
ZOL 5 mg + PTH 20 µg	128	6.31 (0.337)	(ZOL 5 mg + PTH 20 µg) – (Placebo + PTH 20 µg)	1.85 (0.465)	0.94, 2.77	<0.0001
			(ZOL 5 mg + PTH 20 µg) – (ZOL 5 mg)	2.43 (0.466)	1.52, 3.35	<0.0001
Placebo + PTH 20 µg	132	4.45 (0.330)	(Placebo + PTH 20 µg) – (ZOL 5 mg)	0.58 (0.462)	-0.33, 1.49	0.2118
ZOL 5 mg	130	3.87 (0.333)				

ZOL=zoledronic acid; PTH=parathyroid hormone; SE=standard error; LSM = least squares mean, CI = confidence interval

(1) 95% confidence interval is calculated based on a t-distribution.

(2) p-value is obtained from ANOVA with treatment and country as explanatory variables.

Between-treatment comparison for percent change in total hip BMD (excluding missing values) relative to baseline, by visit (ITT population)

Treatment	n	LSM (SE)	Pair-wise treatment comparison	LSM difference	95% CI of LSM difference (1)	p-value (2)
Week 13						
ZOL 5 mg + PTH 20 µg	127	2.54 (0.222)	(ZOL 5 mg + PTH 20 µg) – (Placebo + PTH 20 µg)	1.79 (0.305)	1.19, 2.39	<0.0001
			(ZOL 5 mg + PTH 20 µg) – (ZOL 5 mg)	1.01 (0.305)	0.41, 1.61	0.0010
Placebo + PTH 20 µg	133	0.75 (0.216)	(Placebo + PTH 20 µg) – (ZOL 5 mg)	-0.78 (0.302)	-1.37, -0.19	0.0100
ZOL 5 mg	133	1.53 (0.216)				

Week 26						
ZOL 5 mg + PTH 20 µg	128	2.31 (0.265)	(ZOL 5 mg + PTH 20 µg) – (Placebo + PTH 20 µg)	1.42 (0.364)	0.71, 2.14	0.0001
			(ZOL 5 mg + PTH 20 µg) – (ZOL 5 mg)	0.59 (0.366)	-0.13, 1.31	0.1105
Placebo + PTH 20 µg	133	0.89 (0.259)	(Placebo + PTH 20 µg) – (ZOL 5 mg)	-0.84 (0.363)	-1.55, -0.12	0.0218
ZOL 5 mg	130	1.73 (0.262)				
Week 52						
ZOL 5 mg + PTH 20 µg	123	2.33 (0.312)	(ZOL 5 mg + PTH 20 µg) – (Placebo + PTH 20 µg)	1.23 (0.429)	0.38, 2.07	0.0045
			(ZOL 5 mg + PTH 20 µg) – (ZOL 5 mg)	0.16 (0.429)	-0.68, 1.01	0.7038
Placebo + PTH 20 µg	129	1.10 (0.304)	(Placebo + PTH 20 µg) – (ZOL 5 mg)	-1.06 (0.423)	-1.89, -0.23	0.0125
ZOL 5 mg	129	2.16 (0.303)				

ZOL=zoledronic acid; PTH=parathyroid hormone; SE=standard error; LSM = least squares mean, CI = confidence interval

(1) 95% confidence interval is calculated based on a t-distribution.

(2) p-value is obtained from ANOVA with treatment and country as explanatory variables.

Between-treatment comparison for log (e) P1NP (ng/mL) relative to baseline, by visit (ITT population)

Treatment	n	g-LSM of ratio (1)	Pair-wise treatment comparison	Relative treatment effect (2)	95% CI of ratio (3)	p-value (4)
Week 4						
ZOL 5 mg + PTH 20 µg	109	1.18	(ZOL 5 mg + PTH 20 µg) / (Placebo + PTH 20 µg)	0.67	0.61, 0.73	<0.0001
			(ZOL 5 mg + PTH 20 µg) / (ZOL 5 mg)	1.57	1.43, 1.71	<0.0001
Placebo + PTH 20 µg	104	1.76	(Placebo + PTH 20 µg) / (ZOL 5 mg)	2.34	2.15, 2.56	<0.0001
ZOL 5 mg	110	0.75				
Week 8						
ZOL 5 mg + PTH 20 µg	106	0.74	(ZOL 5 mg + PTH 20 µg) / (Placebo + PTH 20 µg)	0.40	0.35, 0.44	<0.0001
			(ZOL 5 mg + PTH 20 µg) / (ZOL 5 mg)	1.82	1.63, 2.03	<0.0001
Placebo + PTH 20 µg	98	1.87	(Placebo + PTH 20 µg) / (ZOL 5 mg)	4.60	4.10, 5.16	<0.0001
ZOL 5 mg	107	0.41				
Week 26						

ZOL 5 mg + PTH 20 µg	116	0.99	(ZOL 5 mg + PTH 20 µg) / (Placebo + PTH 20 µg)	0.38	0.32, 0.44	<0.0001
			(ZOL 5 mg + PTH 20 µg) / (ZOL 5 mg)	2.95	2.52, 3.44	<0.0001
Placebo + PTH 20 µg	114	2.61	(Placebo + PTH 20 µg) / (ZOL 5 mg)	7.75	6.62, 9.06	<0.0001
ZOL 5 mg	119	0.34				
Week 39						
ZOL 5 mg + PTH 20 µg	110	1.43	(ZOL 5 mg + PTH 20 µg) / (Placebo + PTH 20 µg)	0.54	0.46, 0.64	<0.0001
			(ZOL 5 mg + PTH 20 µg) / (ZOL 5 mg)	3.64	3.08, 4.31	<0.0001
Placebo + PTH 20 µg	110	2.64	(Placebo + PTH 20 µg) / (ZOL 5 mg)	6.72	5.69, 7.95	<0.0001
ZOL 5 mg	115	0.39				
Week 52						
ZOL 5 mg + PTH 20 µg	110	1.78	(ZOL 5 mg + PTH 20 µg) / (Placebo + PTH 20 µg)	0.76	0.64, 0.90	0.0012
			(ZOL 5 mg + PTH 20 µg) / (ZOL 5 mg)	3.96	3.35, 4.68	<0.0001
Placebo + PTH 20 µg	112	2.35	(Placebo + PTH 20 µg) / (ZOL 5 mg)	5.23	4.42, 6.18	<0.0001
ZOL 5 mg	113	0.45				

ZOL=zoledronic acid; PTH=parathyroid hormone; LSM = least squares mean, CI = confidence interval, n = Number of patients with evaluable measurements at both baseline and post-baseline within each efficacy visit window

(1) g-LSM of ratio = the exponential of LSM on log(e)(ratio), i.e., the geometric LSM on the log(e) ratio scale.

(2) Relative treatment effect = the exponential of the LSM difference on log(e)(ratio). For values less than 1, the treatment before the ratio symbol (/) has a greater reduction than the one after.

(3) The 95% CI is calculated by inversing the log(e) ratio transformation.

(4) p-value is obtained from ANCOVA on log(e)(ratio) with treatment, country, and log(e)(baseline) as explanatory variables.

Between-treatment comparison for log (e) b-CTx (ng/mL) relative to baseline, by visit (ITT population)

Treatment	n	g-LSM of ratio (1)	Pair-wise treatment comparison	Relative treatment effect (2)	95% CI of ratio (3)	p-value (4)
Week 4						
ZOL 5 mg + PTH 20 µg	109	0.09	(ZOL 5 mg + PTH 20 µg) / (Placebo + PTH 20 µg)	0.09	0.08, 0.11	<0.0001
			(ZOL 5 mg + PTH 20 µg) / (ZOL 5 mg)	1.22	1.01, 1.47	0.0342
Placebo + PTH 20 µg	104	0.97	(Placebo + PTH 20 µg) / (ZOL 5 mg)	12.95	10.75, 15.61	<0.0001
ZOL 5 mg	110	0.08				
Week 8						

ZOL 5 mg + PTH 20 µg	106	0.17	(ZOL 5 mg + PTH 20 µg) / (Placebo + PTH 20 µg)	0.13	0.11, 0.16	<0.0001
			(ZOL 5 mg + PTH 20 µg) / (ZOL 5 mg)	1.59	1.32, 1.91	<0.0001
Placebo + PTH 20 µg	98	1.25	(Placebo + PTH 20 µg) / (ZOL 5 mg)	11.95	9.90, 14.42	<0.0001
ZOL 5 mg	107	0.10				
Week 26						
ZOL 5 mg + PTH 20 µg	116	0.75	(ZOL 5 mg + PTH 20 µg) / (Placebo + PTH 20 µg)	0.41	0.35, 0.49	<0.0001
			(ZOL 5 mg + PTH 20 µg) / (ZOL 5 mg)	3.32	2.81, 3.94	<0.0001
Placebo + PTH 20 µg	114	1.83	(Placebo + PTH 20 µg) / (ZOL 5 mg)	8.08	6.82, 9.58	<0.0001
ZOL 5 mg	119	0.23				
Week 39						
ZOL 5 mg + PTH 20 µg	110	1.05	(ZOL 5 mg + PTH 20 µg) / (Placebo + PTH 20 µg)	0.56	0.47, 0.66	<0.0001
			(ZOL 5 mg + PTH 20 µg) / (ZOL 5 mg)	3.51	2.96, 4.16	<0.0001
Placebo + PTH 20 µg	110	1.89	(Placebo + PTH 20 µg) / (ZOL 5 mg)	6.32	5.33, 7.50	<0.0001
ZOL 5 mg	115	0.30				
Week 52						
ZOL 5 mg + PTH 20 µg	110	1.25	(ZOL 5 mg + PTH 20 µg) / (Placebo + PTH 20 µg)	0.68	0.58, 0.79	<0.0001
			(ZOL 5 mg + PTH 20 µg) / (ZOL 5 mg)	3.52	3.03, 4.10	<0.0001
Placebo + PTH 20 µg	112	1.85	(Placebo + PTH 20 µg) / (ZOL 5 mg)	5.21	4.49, 6.05	<0.0001
ZOL 5 mg	113	0.35				

ZOL=zoledronic acid; PTH=parathyroid hormone; LSM = least squares mean, CI = confidence interval, n = Number of patients with evaluable measurements at both baseline and post-baseline within each efficacy visit window

(1) g-LSM of ratio = the exponential of LSM on log(e)(ratio), i.e., the geometric LSM on the log(e) ratio scale.

(2) Relative treatment effect = the exponential of the LSM difference on log(e)(ratio). For values less than 1, the treatment before the ratio symbol (/) has a greater reduction than the one after.

(3) The 95% CI is calculated by inversing the log(e) ratio transformation.

(4) p-value is obtained from ANCOVA on log(e)(ratio) with treatment, country, and log(e)(baseline) as explanatory variables.

Safety Results

Adverse Events by System Organ Class

Most frequent treatment-emergent AEs (at least 10% for any group) by primary system organ class (Safety population)

Primary system organ class	Zol 5 mg N=137 n (%)	Zol 5 mg + PTH 20 µg N=137 n (%)	Placebo + PTH 20 µg N=137 n (%)
Total no. of patients with an AE	125 (91.2)	125 (91.2)	117 (85.4)
System organ class			
Musculoskeletal and connective tissue disorders	76 (55.5)	80 (58.4)	61 (44.5)
Infections and infestations	67 (48.9)	55 (40.1)	58 (42.3)
General disorders and administration site conditions	61 (44.5)	70 (51.1)	42 (30.7)
Gastrointestinal disorders	44 (32.1)	59 (43.1)	53 (38.7)
Nervous system disorders	34 (24.8)	38 (27.7)	31 (22.6)
Injury, poisoning and procedural complications	32 (23.4)	30 (21.9)	28 (20.4)
Skin and subcutaneous tissue disorders	21 (15.3)	21 (15.3)	21 (15.3)
Vascular disorders	16 (11.7)	17 (12.4)	18 (13.1)
Psychiatric disorders	14 (10.2)	10 (7.3)	12 (8.8)
Metabolism and nutrition disorders	13 (9.5)	8 (5.8)	16 (11.7)
Cardiac disorders	8 (5.8)	16 (11.7)	7 (5.1)
Respiratory, thoracic and mediastinal disorders	8 (5.8)	14 (10.2)	18 (13.1)

Most frequent treatment-emergent AEs (at least 5% for any group) by preferred term (Safety population)

Preferred term	Zol 5 mg N=137 n (%)	Zol 5 mg + PTH 20 µg N=137 n (%)	Placebo + PTH 20 µg N=137 n (%)
Total no. of patients with an AE	125 (91.2)	125 (91.2)	117 (85.4)
Preferred term			
Arthralgia	30 (21.9)	31 (22.6)	18 (13.1)
Headache	24 (17.5)	24 (17.5)	20 (14.6)
Back pain	23 (16.8)	23 (16.8)	16 (11.7)
Myalgia	22 (16.1)	15 (10.9)	6 (4.4)
Fatigue	18 (13.1)	19 (13.9)	13 (9.5)
Bronchitis	17 (12.4)	5 (3.6)	6 (4.4)
Nasopharyngitis	16 (11.7)	23 (16.8)	20 (14.6)
Nausea	15 (10.9)	21 (15.3)	19 (13.9)
Pain in extremity	15 (10.9)	17 (12.4)	8 (5.8)

Urinary tract infection	14 (10.2)	7 (5.1)	9 (6.6)
Chills	13 (9.5)	16 (11.7)	4 (2.9)
Influenza like illness	13 (9.5)	20 (14.6)	6 (4.4)
Edema peripheral	11 (8.0)	8 (5.8)	7 (5.1)
Fall	9 (6.6)	8 (5.8)	4 (2.9)
Vomiting	9 (6.6)	11 (8.0)	4 (2.9)
Constipation	8 (5.8)	10 (7.3)	8 (5.8)
Pyrexia	8 (5.8)	17 (12.4)	3 (2.2)
Hypertension	7 (5.1)	8 (5.8)	9 (6.6)
Influenza	7 (5.1)	9 (6.6)	4 (2.9)
Musculoskeletal pain	7 (5.1)	7 (5.1)	8 (5.8)
Upper respiratory tract infection	7 (5.1)	5 (3.6)	7 (5.1)
Vertigo	7 (5.1)	5 (3.6)	9 (6.6)
Bone pain	6 (4.4)	8 (5.8)	4 (2.9)
Contusion	6 (4.4)	7 (5.1)	9 (6.6)
Diarrhea	6 (4.4)	5 (3.6)	11 (8.0)
Sinusitis	5 (3.6)	7 (5.1)	1 (0.7)
Dyspepsia	4 (2.9)	4 (2.9)	8 (5.8)
Muscle spasms	4 (2.9)	5 (3.6)	9 (6.6)
Osteoarthritis	4 (2.9)	8 (5.8)	6 (4.4)
Dizziness	3 (2.2)	5 (3.6)	7 (5.1)

Data are sorted by descending frequency, as reported in the ZOL 5 mg group.

Serious Adverse Events and Deaths

Patients who died, had serious or clinically significant AEs, or discontinued because of them (Safety population)

Primary system organ class	Zol 5 mg N=137 n (%)	Zol 5 mg + PTH 20 µg N=137 n (%)	Placebo + PTH 20 µg N=137 n (%)
Total no. of patients with a serious or significant AE	22 (16.1)	22 (16.1)	26 (19.0)
Deaths	1 (0.7)	0 (0.0)	0 (0.0)
SAEs [1]	20 (14.6)	13 (9.5)	15 (10.9)
AE causing discontinuation of study drug	3 (2.2)	11 (8.0)	13 (9.5)
SAE causing discontinuation of study drug	1 (0.7)	1 (0.7)	1 (0.7)
Non-serious AEs causing discontinuation of study drug	2 (1.5)	11 (8.0)	13 (9.5)
AEs causing discontinuation from study	2 (1.5)	5 (3.6)	3 (2.2)
Laboratory abnormalities causing discontinuation from study	0 (0.0)	0 (0.0)	0 (0.0)

[1] death is included

Other Relevant Findings

Pre-specified renal laboratory abnormalities at any time during the study (Safety population)

Lab test	Baseline creatinine clearance level	Zol 5 mg N=137		Zol 5 mg + PTH 20 µg N=137		Placebo + PTH 20 µg N=137	
		N	n (%)	N	n (%)	N	n (%)
Increase in serum creatinine > 0.5 mg/dL							
	< 30	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
	≥ 30 - < 35	2	0 (0.0)	0	0 (0.0)	3	0 (0.0)
	≥ 35 - < 40	2	1 (50.0)	4	0 (0.0)	5	0 (0.0)
	≥ 40 -≤50	15	0 (0.0)	8	0 (0.0)	8	0 (0.0)
	> 50 -60	21	0 (0.0)	25	0 (0.0)	19	0 (0.0)
	> 60	97	1 (1.0)	98	0 (0.0)	102	0 (0.0)
	All patients	137	2 (1.5)	135	0 (0.0)	137	0 (0.0)
Urine protein dipstick > 2+							
	< 30	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
	≥ 30 - < 35	2	0 (0.0)	0	0 (0.0)	3	0 (0.0)
	≥ 35 - < 40	2	0 (0.0)	4	0 (0.0)	5	0 (0.0)
	≥ 40 -≤50	15	0 (0.0)	8	0 (0.0)	8	0 (0.0)
	> 50 -60	21	1 (4.8)	25	0 (0.0)	19	0 (0.0)
	> 60	97	0 (0.0)	98	0 (0.0)	102	0 (0.0)
	All patients	137	1 (0.7)	135	0 (0.0)	137	0 (0.0)
Creatinine clearance < 30 mL/min							
	< 30	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
	≥ 30 - < 35	2	1 (50.0)	0	0 (0.0)	3	1 (33.3)
	≥ 35 - < 40	2	0 (0.0)	4	1 (25.0)	5	0 (0.0)
	≥ 40 -≤50	15	0 (0.0)	8	0 (0.0)	8	0 (0.0)
	> 50 -60	21	0 (0.0)	25	0 (0.0)	19	0 (0.0)
	> 60	97	0 (0.0)	98	0 (0.0)	101	0 (0.0)
	All patients	137	1 (0.7)	135	1 (0.7)	136	1 (0.7)
Creatinine clearance decrease from baseline ≥30% when baseline was ≤60 mL/min							
	< 30	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
	≥ 30 - < 35	2	1 (50.0)	0	0 (0.0)	3	0 (0.0)

≥ 35 - < 40	2	0 (0.0)	4	0 (0.0)	5	0 (0.0)
≥ 40 -≤50	15	0 (0.0)	8	0 (0.0)	8	0 (0.0)
> 50 -60	21	1 (4.8)	25	0 (0.0)	19	0 (0.0)
> 60	3	0 (0.0)	2	0 (0.0)	0	0 (0.0)
All patients	43	2 (4.7)	39	0 (0.0)	35	0 (0.0)

N = the number of patients with evaluable measurements at both baseline and post-baseline.

n = the number of patients meeting the criterion.

Renal laboratory abnormality: Increase from baseline in serum creatinine > 0.5 mg/dL, treatment-emergent protein urine dipstick > 2+, calculated creatinine clearance < 30 mL/min, or calculated creatinine clearance decrease from baseline ≥30%.

For protein urine dipstick, baseline urine dipstick ≤ 2+ was required. For creatinine clearance <30 mL/min, a baseline creatinine clearance ≥30 mL/min was required. For creatinine clearance decrease from baseline ≥30% with baseline value ≤60 mL/min, a baseline creatinine clearance value ≤60 mL/min was required.

Date of Clinical Trial Report

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Date Inclusion on Novartis Clinical Trial Results Database

25-January-2010

Date of Latest Update

21-January-2010