

Summary ID# 10080

Clinical Study Summary: Study B3D-EW-GHCX

Differential Effects of Teriparatide and Strontium Ranelate on Bone Remodeling and Formation in Postmenopausal Women with Osteoporosis: A Histomorphometric Study

Date summary approved by Lilly: 14 January 2008

Brief Summary of Results

This was a Phase 4, multicenter, open-label, randomized active-comparator trial of the histomorphometric effects of teriparatide 20 µg/day subcutaneous injection (s.c.) with those of oral strontium ranelate 2 g/day in the treatment of postmenopausal women with osteoporosis. All patients received approximately 1000 mg/day elemental calcium and approximately 800 IU/day of Vitamin D.

The primary objective of the study was to compare the bone formation activity, measured by the mineralization surface per bone surface (MS%BS), in trans-iliac crest bone biopsies from postmenopausal women with osteoporosis following 6 months of treatment with either teriparatide or strontium ranelate.

The secondary objectives were to compare the effects of teriparatide and strontium ranelate on histomorphometric parameters of bone formation and resorption, structural parameters of cortical and trabecular bone and biochemical markers of bone turnover including markers of bone formation: serum aminoterminal propeptide of type I procollagen [P1NP] and bone-specific alkaline phosphatase [BSAP], and bone resorption: serum type I collagen degradation fragments [β -CTX].

The key results of the study are as follows:

- There were no statistically significant differences between the teriparatide and strontium ranelate groups for the mean MS%BS of trabecular or endocortical bone in the trans-iliac crest bone biopsies after 6 months of treatment ($p=0.219$ and 0.052 , respectively).
- There were no statistically significant differences between the teriparatide and strontium ranelate groups for the secondary efficacy histomorphometric parameters measuring bone formation and resorption activity following 6 months of treatment.
- There was a statistical difference in cortical porosity which was higher in the teriparatide group than the strontium ranelate group ($p=0.037$) after 6 months.
- After 6 months of treatment the percent increases from baseline in median values in the biochemical markers of bone formation, P1NP and BSAP, and resorption, β CTx, for the teriparatide group and the percent decrease in P1NP for the strontium ranelate group were statistically significant ($p<0.001$ for all). There were statistically significant differences in the median percent changes from baseline in P1NP ($p<0.001$ and BSAP ($p=0.005$) and β CTx ($p<0.001$) between the two treatment groups after 6 months.
- No abnormalities were observed in the bone biopsies from patients in either treatment group.
- Serious adverse events were experienced by 1 patient in the teriparatide group (benign parathyroid tumour) and 3 patients in the strontium ranelate group (lymphoma, fractured patella, and cerebrovascular accident). The cerebrovascular accident was thought possibly related to strontium ranelate treatment.
- There was a statistically significant difference in the number of patients with Treatment Emergent Adverse Events (TEAEs) which was higher in the strontium ranelate than the teriparatide group ($p=0.013$). There was no significant difference in TEAEs possibly related to treatment between the two groups ($p=0.154$).
- There were no statistically significant differences between the TEAEs thought possibly related to treatment in the teriparatide and strontium ranelate groups.

Title of Study: Differential Effects of Teriparatide and Strontium Ranelate on Bone Remodeling and Formation in Postmenopausal Women with Osteoporosis: A Histomorphometric Study.	
Investigator(s): This multicenter study included 12 principal investigators.	
Study Center(s): This study was conducted at 12 study centers in 6 countries.	
Length of Study: Date first patient enrolled: 9 November 2005 Date last patient completed: 24 January 2007	Phase of Development: 4

Objectives: The primary objective of this study was to compare the bone formation activity, measured by the mineralization surface per bone surface (MS%BS), in trans-iliac crest bone biopsies from postmenopausal women with osteoporosis following 6 months of treatment with either teriparatide 20 µg/day or strontium ranelate 2 g/day.

The secondary objectives were to compare the effects of teriparatide 20 µg/day and strontium ranelate 2 g/day after 6 months of treatment on:

- Dynamic histomorphometric parameters of bone formation and resorption.
- Structural (static) parameters of cortical and trabecular bone.
- Biochemical markers of bone turnover including markers of bone formation: serum aminoterminal propeptide of type I procollagen [P1NP] and bone-specific alkaline phosphatase [BSAP], and bone resorption: serum type I collagen degradation fragments [β-CTx].
- Safety as determined by absence of primary mineralization defects, woven bone, and other histological anomalies, and clinical adverse events reports.

Study Design: This was a Phase 4, multicenter, open-label, randomized active-comparator trial to compare the histomorphometric effects of teriparatide 20 µg/day s.c. with oral strontium ranelate 2 g/day in the treatment of postmenopausal women with osteoporosis. All patients received approximately 1000 mg/day elemental calcium and approximately 800 IU/day of Vitamin D. The study design is illustrated in Figure 1.

Number of Patients:

Planned: 68 patients

Randomized: 40 teriparatide, 40 strontium ranelate

Treated: : 39 teriparatide, 40 strontium ranelate

Completed: 33 teriparatide, 32 strontium ranelate

Completed with evaluable biopsy: 29 teriparatide, 22 strontium ranelate

Diagnosis and Main Criteria for Inclusion: Patients included in the study, were ambulatory, postmenopausal women aged 45 to 90 years with osteoporosis as determined by bone mineral density (BMD) criteria (with or without prevalent fragility fractures) and with a last menstrual period or bilateral oophorectomy at least 5 years prior to entry. The posterior-anterior lumbar spine (L-1 through L-4) BMD and/or femoral neck BMD and/or total hip BMD measurements were at least 2.5 standard deviations (SD) below the average bone mass for young women. Patients had no severe or chronically disabling conditions other than osteoporosis and normal or clinically insignificantly abnormal laboratory values including serum calcium, PTH(1-84), and alkaline phosphatase and were able to use a pen-type injection delivery system satisfactorily. They were excluded if they had a history of unresolved skeletal diseases that affected bone metabolism other than postmenopausal osteoporosis, active liver disease or significantly impaired renal function, and current or past treatment with any bisphosphonate, parathyroid hormone or its analogs, androgens or other anabolic steroids.

Test Product, Dose, and Mode of Administration:

Teriparatide 20 µg was given once per day via a prefilled injection delivery system (pen-injector). Each pen-injector contained sufficient teriparatide for a 28-day supply given subcutaneously and could be used for up to 28 days after the first injection. Patients were instructed to store the pen injectors containing teriparatide in the refrigerator at 2°C to 8°C (36°F to 46°F).

Duration of Treatment: 6 months

Reference Therapy, Dose, and Mode of Administration:

Strontium ranelate 2g given orally once per day was provided in a sachet for suspension. Patients were instructed to separate the administration of strontium ranelate and food and calcium supplements by at least two hours.

All patients taking either teriparatide or strontium ranelate also received approximately 1000 mg/day of elemental calcium and approximately 800 IU/day Vitamin D supplied by Lilly as open-label supplements for a minimum of 1 month prior to baseline and for the duration of the study. The dosage or formulation of the supplements could be changed, or discontinued if the subject did not tolerate the calcium or Vitamin D

due to gastrointestinal or other symptoms.

Variables:

Efficacy: The primary efficacy measure was the mineralization surface (MS%BS), which reflects the percentage of cancellous surface that is being actively mineralized (i.e. the proportion of the cancellous surface covered by newly formed osteoid), evaluated in double tetracycline stained bone biopsies. The most accurate calculation of MS%BS was obtained by dividing the area of double-label surfaces plus one-half the area of single-label surfaces by the total bone surface area. Secondary efficacy measures included other routine histomorphometric parameters and biochemical markers of bone remodeling.

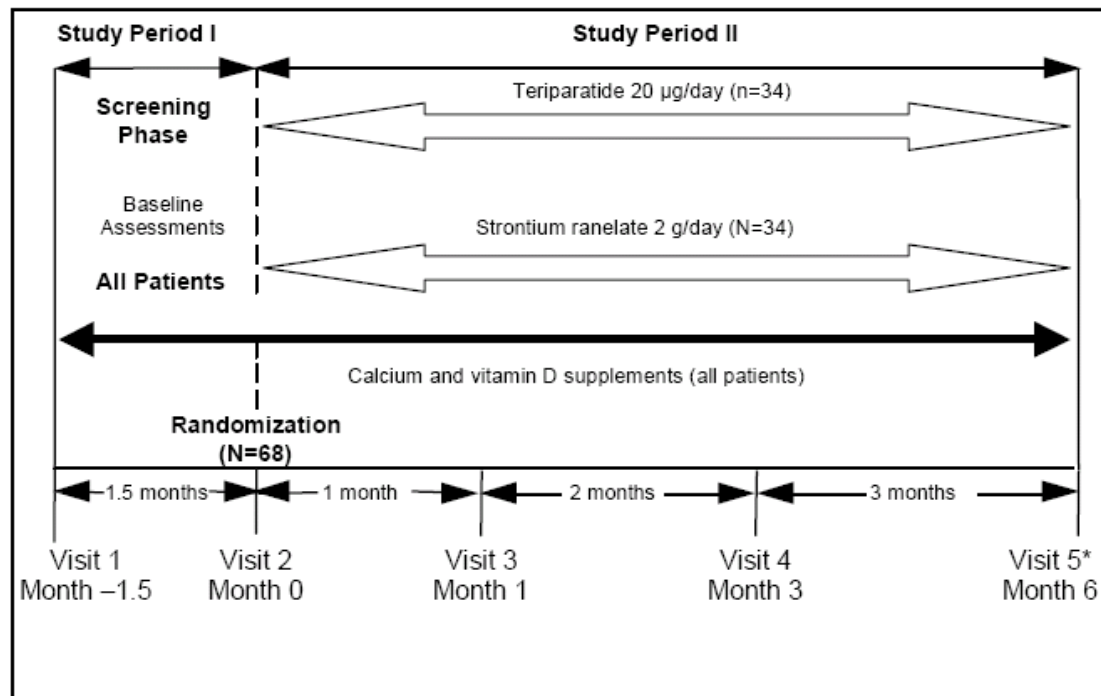
Safety: Prior to enrollment, study site personnel recorded the occurrence and nature of preexisting condition(s) and during the study any change in the condition(s) and occurrence and any adverse events were recorded. Serious adverse events including death, initial or prolonged inpatient hospitalization, a life-threatening experience (that is, immediate risk of dying), persistent or significant disability/incapacity, congenital anomaly/birth defect were recorded. Standard laboratory tests including chemistry, hematology, and urinalysis panels were performed.

Methods:

Statistical: The measurements of MS%BS were analyzed using a one-way ANOVA model with a fixed effect for assigned treatment. The primary analysis used Monte Carlo simulation to derive the p-value for the two-sample t-test. All analyses were based on the intent-to-treat principle. All statistical tests were two-sided and utilized a significance level of 5%. Patient characteristics were summarized by treatment group and overall. Descriptive statistics for continuous variables included the number of patients and mean and standard deviation. Descriptive statistics for categorical variables included frequencies and percentages.

Bioanalytical: Blood serum samples were assayed by an electrochemiluminescence immunoassay for the bone markers procollagen type 1 amino-terminal propeptide (P1NP) and type I collagen degradation fragments (β -CTX) and by an activity-based immunoassay for bone specific alkaline phosphatase (BSAP). Biopsy samples were assessed for the appearance of cellular components, the presence or absence of woven bone, osteomalacia, marrow fibrosis and any other notable features. Inductively coupled plasma atomic emission spectrometry or atomic absorption spectrometry methods were used to ensure an accurate assessment of blood calcium concentrations. Active bone forming, tetracycline-labeled osteons on trabecular and endocortical surfaces were analyzed using polarized light for collagen orientation and cement line stains.

Study Design



*22-24 days before V5, patients were contacted by the investigational site and instructed on the schedule for tetracycline label sequence.

Figure 1. Illustration of study design for Study B3D-EW-GHCX.

Results:

Patient Demographics

Table 1 summarizes the baseline demographic characteristics of all patients who were enrolled in this study. The mean age of the women was 65.4 years in the teriparatide group (n=39) and 63.9 years in the strontium ranelate group (n=40). Mean body mass index (BMI) was 26.07 kg/m² in the teriparatide group and 25.89 kg/m² in the strontium ranelate group and the mean time since menopause was 17.8 years in the teriparatide group and 17.7 years in the strontium ranelate group. Of those patients who had sufficiently low BMD to meet the inclusion criteria, 83.5% had bone mineral density (BMD) measurements for lumbar spine, 45.6% for femoral neck and 17.7% for total hip.

For all patients, the mean T-scores for lumbar spine were -3.04 in the teriparatide and -3.18 in the strontium ranelate group, for total hip -1.76 in the teriparatide and -1.88 in the strontium ranelate group and for femoral neck -2.49 in the teriparatide and -2.30 in the strontium ranelate group. There were no statistically significant differences in baseline characteristics between the two groups.

**Table 1. Patient Demographics at Baseline
All Randomized Treated Patients (FAS*)**

	Descriptive Statistics						Between treatment comparison		
							Adjusted	Standard	P-value[a]
	N	Mean	SD	Min	Median	Max	Mean	Error	Therapy
Age (years)									0.409
Teriparatide	39	65.4	8.00	51	65.0	79	65.3	1.28	
Strontium	40	63.9	7.55	49	63.5	85	63.8	1.31	
Overall	79	64.6	7.77	49	64.0	85			
Body mass index (kg/m²)									0.821
Teriparatide	39	26.07	4.343	18.7	25.50	38.9	26.06	0.678	
Strontium	40	25.89	3.944	19.9	25.45	36.5	25.85	0.694	
Overall	79	25.98	4.120	18.7	25.50	38.9			
Years postmenopausal									0.900
Teriparatide	38	17.8	9.44	5	17.0	35	17.2	1.43	
Strontium	39	17.7	7.63	4	17.0	33	17.0	1.46	
Overall	77	17.8	8.51	4	17.0	35			
Lumbar Spine t-score									0.175
Teriparatide	33	-3.04	0.658	-4.9	-3.00	-0.9	-3.0	0.10	
Strontium	36	-3.18	0.497	-4.4	-3.15	-2.0	-3.2	0.10	
Overall	69	-3.11	0.580	-4.9	-3.07	-0.9			
Total Hip t-score									0.490
Teriparatide	32	-1.76	0.801	-3.2	-1.75	0	1.8	0.15	
Strontium	33	-1.88	0.819	-4.1	-1.70	-0.7	1.9	0.15	
Overall	65	-1.82	0.806	-4.1	-1.70	0			
Femoral Neck t-score									0.447
Teriparatide	39	-2.49	0.962	-4.5	2.40	0.3	-2.5	0.13	
Strontium	40	-2.30	0.831	-4.4	2.30	0.2	-2.4	0.14	
Overall	79	-2.40	0.897	-4.5	2.30	0.2			

[a] Continuous Variable Model Variable=Therapy + Country, Type III estimates and P-values are provided.

*FAS=full analysis set

There were no statistically significant between-group differences in the levels of P1NP and BSAP, the markers of bone formation, or serum β CTx, a marker of bone resorption, at baseline (Table 2).

**Table 2. Baseline Biochemical Markers of Bone Metabolism
All Randomized Treated Patients (FAS)**

	Descriptive Statistics							Comparison
								P-value[a]
	N	Mean	SD	Min	Median	Max	IQR (25%; 75%)	Therapy
PlNP (µg/L)								0.942
Teriparatide	39	47.03	17.368	15.6	49.00	107.2	(34.90; 58.80)	
Strontium	39	50.77	23.633	25.7	46.40	146.2	(36.40; 59.80)	
Overall	78	48.90	20.689	15.6	47.75	146.2	(36.40; 58.80)	
BSAP (µg/L)								0.788
Teriparatide	39	11.81	4.479	4.6	11.30	24.2	(8.70; 15.00)	
Strontium	39	11.01	3.952	4.3	10.70	21.0	(8.90; 13.10)	
Overall	78	11.41	4.215	4.3	10.75	24.2	(8.80; 13.90)	
CTx (µg/L)								0.565
Teriparatide	39	378.62	189.673	104.0	367.00	1126.0	(231.00; 495.00)	
Strontium	39	389.85	155.457	79.0	396.00	894.0	(266.00; 469.00)	
Overall	78	384.23	172.374	79.0	377.00	1126.0	(255.00; 469.00)	

[a] Ranked values were compared between countries using the ANOVA model RANK=Country. Residuals from this model were then analyzed using a two-sample Wilcoxon Test (i.e. an aligned rank analysis).

Anti-osteoporosis agents had been taken by 2.6% of patients in the teriparatide group and 12.5% in the strontium ranelate group ($p=0.083$). There were no statistically significant differences in history of prior fracture between the two treatment groups.

Patient Disposition

A total of 80 patients were enrolled in the study, and 39 received at least one dose of teriparatide and 40 of strontium ranelate. Of these, 65 (82.3%; teriparatide: $n=33$, strontium ranelate: $n=32$) completed treatment and 51 (64.6%; teriparatide: $n=29$, strontium ranelate: $n=22$) had an evaluable biopsy.

Figure 2 and Table 3 summarize reasons for discontinuation. Fourteen (17.7%) patients discontinued (teriparatide: 15.4%, strontium ranelate: 20.0%); 6 were due to an adverse event, 6 were patient decision, and for 2 patients the protocol entry criteria were not met.

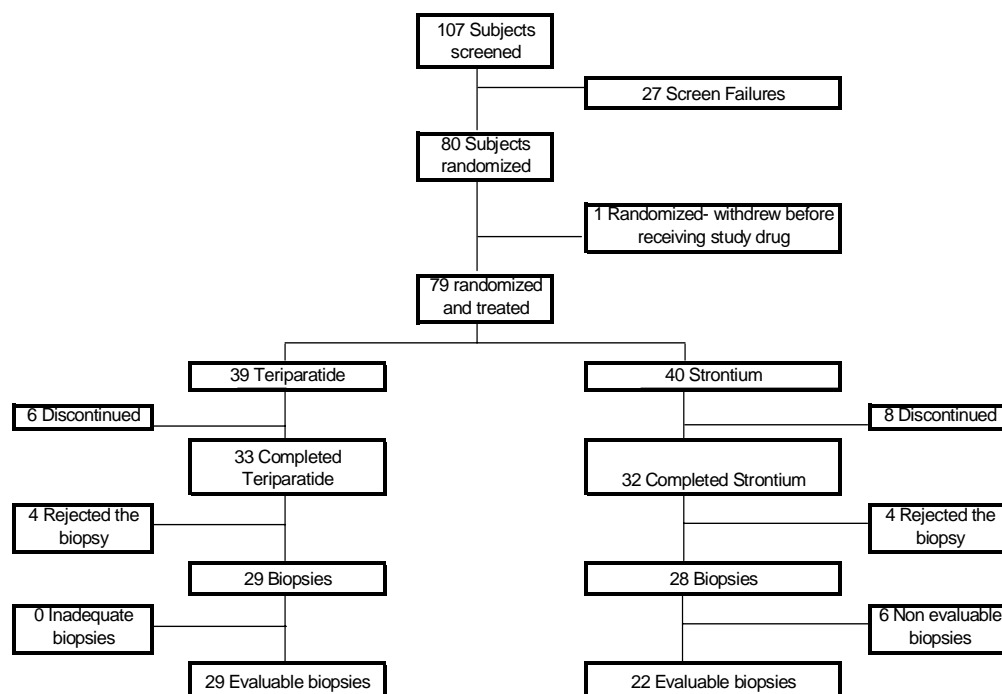


Figure 2. Patient disposition.

Table 3. Patient Disposition: Between-Group Comparisons

	Overall	Teriparatide	Strontium	P-value [a]
Treated [b]	79 (100)	39 (100)	40 (100)	
Completed treatment	65 (82.3)	33 (84.6)	32 (80.0)	
Completed with evaluable biopsy	51 (64.6)	29 (74.4)	22 (55.0)	0.100
Treated withdrawn	14 (17.7)	6 (15.4)	8 (20.0)	0.7695
Adverse event	6 (7.6)	2 (5.1)	4 (10.0)	0.675
Patient decision	6 (7.6)	3 (7.7)	3 (7.5)	1.000
Protocol entry criteria not met	2 (2.5)	1 (2.6)	1 (2.5)	1.000

[a] Discontinuation rates between treatment groups were compared for each type of discontinuation using Fisher's Exact Test.

[b] Randomized and treated patients form the Full Analysis Set for Patient Disposition.

Primary Efficacy Variable

Table 4 summarizes the details of bone formation, as MS%BS in the trans-iliac crest bone biopsies, following treatment for 6 months with teriparatide and strontium ranelate. The mean (\pm SE) trabecular MS%BS values in the teriparatide ($7.73\% \pm 1.484$) and strontium ranelate ($5.25\% \pm 1.146$) groups were not statistically different (2-sample T-test with Monte Carlo simulation, $p=0.219$). The mean (\pm SE) endocortical MS%BS values in the teriparatide ($17.22\% \pm 3.055$) and strontium ranelate ($9.70\% \pm 2.074$) groups were not statistically different ($p=0.052$).

Table 4. Histomorphometric Parameters of Bone Formation: Trabecular and Endocortical Mineralizing Surfaces (%) Patients with Evaluable Biopsy Data (FAS)

Descriptive Statistics								T-test [a]		RankSum [b]	
	N	Mean	StdErr	SD	Min	Median	Max	PTH-STR	P-val	PTH-STR	P-val
Trabecular mineralizing surface (%)								2.477	0.219	1.145	0.281
Teriparatide	28	7.73	1.484	7.850	0.5	4.30	36.1				
Strontium	22	5.25	1.146	5.374	0.3	3.29	25.7				
Endocortical mineralizing surface (%)								7.514	0.052	5.950	0.040
Teriparatide	27	17.22	3.055	15.872	1.3	14.50	78.1				
Strontium	22	9.70	2.074	9.727	0.4	6.65	37.3				

Abbreviations: BS=bone surface; BV=bone volume SD=standard deviation; StdErr=standard error; Max=maximum; Min=minimum; PTH=teriparatide; P-val=p-value; STR=strontium.

[a] Two-sample t-test with Monte Carlo simulation for the two-sided p-value. Estimate is the observed difference in mean values.

[b] Two-sample Rank Sum test with Monte Carlo simulation for the two-sided p-value. Estimate is the Hodges-Lehman estimator.

Secondary Efficacy Variables

Histomorphometry:

- There were no statistically significant between-group differences in histomorphometric dynamic parameters of bone following treatment with either teriparatide or strontium ranelate ($p>0.05$).
- There were no statistically significant differences in the structural parameters of cortical and trabecular bone between the treatment groups with the exception of cortical porosity, which was statistically different between the teriparatide group (mean \pm SE: $5.40\% \pm 0.411$) and the strontium ranelate group ($4.14\% \pm 0.403$; $p=0.037$).

Biochemical markers

- In the teriparatide group, the percent increases in median values from baseline for the biochemical marker of bone formation P1NP were statistically significant at all time points ($p<0.001$) and in the strontium ranelate group the median values for percent decreases in P1NP from baseline were statistically significant after 3 ($p=0.005$) and 6 ($p<0.001$) months.
- In the teriparatide group, for the bone formation marker BSAP, the percent increase after 6 months was statistically significant ($p<0.001$) and in the strontium ranelate group there were no statistically significant changes.
- In the teriparatide group, the percent increases for the biochemical marker of bone resorption (β CTx) were statistically significant at all time points ($p<0.001$) and in the strontium ranelate group there were statistically significant percent decreases after 1 ($p=0.029$) and 3 ($p=0.040$) months but not at 6 months ($p=0.701$).

Safety

Extent of Exposure

The mean extent of exposure and days on the drug for the full analysis set were not statistically significantly different between patients in the teriparatide ($n=39$; mean \pm SD: 163.2 ± 46.27 days and 166.4 ± 47.44 days, respectively) and strontium ranelate ($n=39$; mean \pm SD: 164.2 ± 42.89 days and 167.4 ± 44.24 days, respectively) groups. For patients with evaluable biopsy data, the extent of exposure was 179.1 ± 9.98 days for teriparatide and 183.5 ± 14.50 days for strontium ranelate ($p=0.332$) and days on the drug were 183.1 ± 10.04 for teriparatide and 187.5 ± 14.50 for strontium ranelate ($p=0.329$). Overall, for the randomized treated patients, 89.7% of patients in the teriparatide group and 92.5% of patients in the strontium ranelate group were treatment compliant where compliance was defined as greater than or equal to 85% of the recommended dose. At

the time of the biopsy there were no statistically significant differences between the mean doses of calcium and vitamin D between the two groups.

Adverse Event Profile

Details of Treatment-Emergent Adverse Events (TEAEs) that occurred in $\geq 5\%$ of either teriparatide or strontium ranelate-treated patients in this study are presented in Table 5 by body system organ class and preferred term (MedDRA version 10.0). There were statistically more patients with TEAEs in the strontium ranelate (n=28) than in the teriparatide (n=16) group (p=0.013). In the teriparatide group, back pain was reported by 2 patients with no other TEAE reported more than once. In the strontium ranelate group the most common TEAEs were procedural pain, related to the bone biopsy procedure, and hypercholesterolemia (n=4 in each), incident fracture and hypertension (n=3 for each) and dyspepsia, rib fracture, back pain and headache (n=2 for each) were reported. TEAEs were thought possibly related to teriparatide treatment for 2 (5.1%) patients (dyspepsia, nausea, abdominal pain) and to strontium ranelate treatment for 7 (17.5%) patients (dyspepsia, upper abdominal pain, nausea, diarrhoea, frequent bowel movements, cerebrovascular accident, dry throat, rash). In the teriparatide group 38.5% of patients had TEAEs of mild severity and 2.6% had TEAEs that were severe. In the strontium ranelate group 51.3% of patients had TEAEs that were of mild severity, 17.9% had TEAEs of moderate severity, and 2.6% had TEAEs that were severe.

Table 6 summarizes the SAEs reported during this study. One patient in the teriparatide group and 3 patients in the strontium ranelate group had one reported SAE each. These SAEs were a benign parathyroid tumor in the teriparatide group and a lymphoma, fractured patella and cerebrovascular accident in the strontium ranelate group. The cerebrovascular accident was thought possibly related to strontium ranelate. There were no deaths in this study.

As shown in Table 7, 2 patients in the teriparatide group and 4 patients in the strontium ranelate group withdrew due to TEAEs (teriparatide: abdominal pain, benign parathyroid tumor; strontium ranelate: upper abdominal pain, dyspepsia, lymphoma, rash). Of these patients, 1 in the teriparatide group with abdominal pain and 3 in the strontium ranelate group with upper abdominal pain, dyspepsia and rash were thought to be drug-related.

**Table 5. Adverse Events Occurring in $\geq 5\%$ of Patients
All Randomized Patients (FAS)**

Body system Preferred term	Teriparatide (FAS = 39)			Strontium (FAS = 40)			Treatment Comparison Pvalue [a]
	n	(%)	events	n	(%)	events	
Overall							
Patients with ≥ 1 TEAE	16	(41.0)	26	28	(70.0)	54	0.013
Gastrointestinal disorders							
Patients with ≥ 1 TEAE	4	(10.3)	5	7	(17.5)	8	0.518
Dyspepsia	1	(2.6)	1	2	(5.0)	2	
Infections and infestations							
Patients with ≥ 1 TEAE	3	(7.7)	3	5	(12.5)	6	0.712
Injury, poisoning and procedural complications							
Patients with ≥ 1 TEAE	1	(2.6)	1	7	(17.5)	9	0.057
Procedural pain	1	(2.6)	1	4	(10.0)	4	
Total incident fracture	0			3	(7.5)	3	
Rib fracture	0			2	(5.0)	2	
Musculoskeletal and connective tissue disorders							
Patients with ≥ 1 TEAE	4	(10.3)	7	4	(10.0)	4	1.000
Back pain	2	(5.1)	2	2	(5.0)	2	
Metabolism and nutrition disorders							
Patients with ≥ 1 TEAE	1	(2.6)	2	5	(12.5)	5	0.201
Hypercholesterolaemia	1	(2.6)	1	4	(10.0)	4	
Nervous system disorders							
Patients with ≥ 1 TEAE	0			5	(12.5)	5	0.055
Headache	0			2	(5.0)	2	
Vascular disorders							
Patients with ≥ 1 TEAE	1	(2.6)	2	3	(7.5)	3	0.615
Hypertension	1	(2.6)	1	3	(7.5)	3	
Cardiac disorders							
Patients with ≥ 1 TEAE	0			3	(7.5)	3	0.241
Neoplasms benign, malignant and unspecified (incl cysts and polyps)							
Patients with ≥ 1 TEAE	1	(2.6)	1	2	(5.0)	2	1.000
Immune system disorders							
Patients with ≥ 1 TEAE	0			2	(5.0)	2	0.494

[a] Treatments compared using two-sided Fisher's Exact Test. P-values presented for Body Systems and any significant ($p < 0.05$) preferred term.

**Table 6. Serious Adverse Events
All Randomized Patients (FAS)**

Body system Preferred term	Teriparatide	Strontium	All Serious TEAE					Possibly-related Serious TEAE [a]				
			Fisher's		Teriparatide		Test P-value	Fisher's		(FAS = 40)		Test P-value
			(FAS = 39)		(FAS = 40)			(FAS = 39)		(FAS = 40)		
			n	(%)	n	(%)	[b]	n	(%)	n	(%)	[b]
Overall												
Patients with ≥1 Serious TEAE			1	(2.6)	3	(7.5)	0.615	0		1	(2.5)	1.000
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												
Patients with ≥1 Serious TEAE			1	(2.6)	1	(2.5)	1.000					
Lymphoma			0		1	(2.5)						
Parathyroid tumor benign			1	(2.6)	0							
Injury, poisoning and procedural complications												
Patients with ≥1 Serious TEAE			0		1	(2.5)	1.000					
Patella fracture			0		1	(2.5)						
Nervous system disorders												
Patients with ≥1 Serious TEAE			0		1	(2.5)	1.000	0		1	(2.5)	1.000
Cerebrovascular accident			0		1	(2.5)		0		1	(2.5)	

[a] Possible relationship to study medication determined by the investigator.

[b] Treatments compared using two-sided Fisher's Exact Test. P-values presented for Body Systems and any significant (p<0.05) preferred term.

**Table 7. Adverse Events Leading to Discontinuation
All Randomized Patients (FAS)**

Body system Preferred term	All TEAE that led to withdrawal			Possibly-related and led to withdrawal[a]		
	Teriparatide (FAS = 39)		Fisher's Test P-value [b]	Teriparatide (FAS = 39)		Fisher's Test P-value [b]
	n	(%)		n	(%)	
Overall						
Patients with ≥1 TEAE	2	(5.1)	0.675	1	(2.6)	0.615
Gastrointestinal disorders						
Patients with ≥1 TEAE	1	(2.6)	1.000	1	(2.6)	1.000
Abdominal pain	1	(2.6)		1	(2.6)	
Abdominal pain upper	0			0		
Dyspepsia	0			0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Patients with ≥1 TEAE	1	(2.6)	1.000			
Lymphoma	0					
Parathyroid tumor benign	1	(2.6)				
Skin and subcutaneous tissue disorders						
Patients with ≥1 TEAE	0		1.000	0		1.000
Rash	0			0		

[a] Possible relationship to study medication determined by the investigator.

[b] Treatments compared using two-sided Fisher's Exact Test. P-values presented for Body Systems and any significant ($p < 0.05$ preferred term).

Clinical Laboratory Tests

Table 8 summarises changes in mean clinical chemistry values and the statistical significance of these changes between teriparatide and strontium ranelate treatments. There were statistically significant differences in the increases in levels of alkaline phosphatases ($p<0.001$), serum creatinine ($p=0.018$), uric acid ($p<0.001$), calcium ($p<0.001$), and mean cell hemoglobin ($p=0.016$). The levels were higher in the teriparatide treatment group compared with the strontium ranelate group. There was a statistically significant increase in mean serum creatine kinase levels from baseline in the strontium ranelate group ($p=0.016$). The change was not statistically significant in the teriparatide group ($p=0.323$). The values remained within the normal range and when compared between treatment groups, the changes were not statistically significant ($p=0.094$).

In the teriparatide group serum creatinine levels in one patient and uric acid levels in 3 patients were reported as markedly abnormal. One patient in the strontium ranelate group had markedly abnormal platelets. There were no statistically significant changes from baseline to endpoint in urine analyses.

Vital Signs and Bone Biopsies

There were no statistically significant changes from baseline or between treatment groups in pulse rate or diastolic and systolic blood pressure. There was a statistically significant increase in BMI from 26.1 kg/m^2 to 26.6 kg/m^2 in the teriparatide treatment group ($p=0.017$). The BMI after 6 months was not statistically significantly different from patients in the strontium ranelate group ($p=0.175$). There were no abnormalities observed in the bone biopsies in either treatment group.

Table 8. Clinical Serum Chemistry and Hematology

Variable Timepoint	Teriparatide [a]				Strontium [a]				Treatment contrast [a,b]				Baseline Covariate P-value
	N	Adj. mean	Std Err	Within P-value	N	Adj. mean	Std Err	Within P-value	Std Est.	Between Err	P-value	95% CI	
Alkaline phosphatases (U/L)													
Baseline	39	83.60	3.857		40	80.81	3.950		2.79	5.326	0.602	(-7.82, 13.41)	
Month 6	33	102.00	2.961	<0.001	32	83.82	3.008	0.776	18.18	4.260	<0.001	(9.67, 26.70)	<0.001
Blood urea nitrogen (mmol/L)													
Baseline	39	6.07	0.261		40	5.53	0.267		0.55	0.360	0.1335	(-0.17, 1.26)	
Month 6	33	6.37	0.237	0.466	32	5.21	0.241	0.119	1.16	0.343	0.001	(0.47, 1.84)	0.002
Serum creatinine (umol/L)													
Baseline	39	69.73	1.869		40	69.59	1.915		0.15	2.581	0.955	(-5.00, 5.29)	
Month 6	33	75.25	1.525	0.007	32	70.47	1.549	0.869	4.78	2.176	0.032	(0.43, 9.13)	<0.001
Uric acid (mmol/L)													
Baseline	39	0.26	0.011		40	0.27	0.011		-0.01	0.015	0.329	(-0.04, 0.02)	
Month 6	33	0.32	0.007	<0.001	32	0.27	0.007	0.491	0.05	0.011	<0.001	(0.03, 0.07)	<0.001
Calcium (mmol/L)													
Baseline	39	2.36	0.021		40	2.37	0.022		-0.01	0.030	0.837	(-0.07, 0.05)	
Month 6	33	2.50	0.021	<0.001	32	2.34	0.021	0.028	0.16	0.030	<0.001	(0.10, 0.22)	0.004
Creatine kinase (U/L)													
Baseline	39	87.86	6.617		40	75.64	6.777		12.21	9.137	0.1855	(-6.00, 30.43)	
Month 6	33	87.09	14.473	0.323	32	122.47	14.701	0.016	-35.37	20.776	0.094	(-76.90, 6.16)	0.113
Erythrocyte count (10 ¹² /L)													
Baseline	39	4.54	0.063		40	4.55	0.065		-0.01	0.087	0.891	(-0.19, 0.16)	
Month 6	31	4.38	0.042	<0.001	32	4.50	0.041	0.0425	-0.12	0.059	0.049	(-0.24, -0.00)	<0.001
Mean Cell Hemoglobin (pg)													
Baseline	39	30.33	0.305		39	30.48	0.319		-0.15	0.426	0.726	(-1.00, 0.70)	
Month 6	31	30.89	0.153	0.0341	32	30.34	0.153	0.366	0.55	0.216	0.014	(0.11, 0.98)	<0.001