Document title	**Clinical Study Report Synopsis**
Study title	**The efficacy and safety of 2 g strontium ranelate in the treatment of male osteoporosis.** **A prospective multicentric international double-blind placebo controlled study with a treatment duration of 2 years and the main statistical analysis after 1 year.** **MALEO** **First Report M0-M12 analysis**
Study drug	**Strontium ranelate (S 12911)**
Studied indication	**Male osteoporosis**
Development phase	**Phase III**
Protocol code	**CL3-12911-032**
Study initiation date	**11 December 2007**
Study completion date	**05 March 2010**
Main coordinator	[redacted] **Belgium**
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **6 place des Pleiades** **92415 Courbevoie Cedex - France** **Servier Canada Inc.** **235 Armand-Frappier Blvd** **Laval, Quebec - Canada H7H 4A7** **Laboratorios Servier, S.L.** **Avenida de los Madronos, 33** **28043 Madrid - Spain** **Servier Research and Development** **Gallions, Wexham Springs** **Framewood Road - Wexham** **Slough SL3 6RJ - United Kingdom**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 17 December 2010**

~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study:
The efficacy and safety of 2 g strontium ranelate in the treatment of male osteoporosis. A prospective multicentric international double-blind placebo controlled study with a treatment duration of 2 years and the main study analysis after 1 year. "The MALEO study"
Protocol No.: CL3-12911-032
First report: M0-M12 analysis

International Coordinator: [redacted] Belgium.

Study centres:
Multicentric study (54 active centres, 14 countries, 261 patients included).
Australia (4 centres, 14 patients), Belgium (2 centres, 25 patients), Canada (4 centres, 19 patients), France (4 centres, 14 patients), Germany (5 centres, 24 patients), Hungary (4 centres, 23 patients), Italy (5 centres, 21 patients), Netherlands (2 centres, 6 patients), Poland (5 centres, 35 patients), Russian federation (5 centres, 31 patients), South Africa (5 centres, 11 patients), Spain (4 centres, 26 patients), Sweden (3 centres, 7 patients), United Kingdom (2 centres, 5 patients).

Publication (reference): Not applicable

Studied period: Initiation date: 11 December 2007 Completion date at M12: 05 March 2010	**Phase of development of the study:** III

Objectives:
The **main objective** of the study was to demonstrate the efficacy over a one-year period of 2 g strontium ranelate compared to placebo in men with osteoporosis on Bone Mineral Density (BMD) at the lumbar spine (L2-L4) similar to that observed in postmenopausal women.
The **secondary objectives** of the study were to determine the efficacy on hip BMD and bone markers and the safety of strontium ranelate over 1 year compared to placebo in men with osteoporosis.

Strontium ranelate efficacy and safety were secondarily assessed in the same way over 2 years (results will be presented in a complementary report).

Methodology:
Multicentric, international, randomised, unbalanced (2:1), double-blind, placebo-controlled study.
Treatment period of two years in 2 parallel groups, one assigned to S 12911 and the other one to placebo.

Number of patients:
Planned: 221 patients (147 patients in the S 12911 group and 74 patients in the placebo group).
Included: 261 included patients (174 patients in the S 12911 group and 87 patients in the placebo group).

Diagnosis and main criteria for inclusion:
To be included in the study, patients were to fulfil the following criteria:

- BMD criteria were similar to those of postmenopausal women included in previous phase III studies SOTI and TROPOS:
  Mean lumbar spine (L2-L4) BMD ≤ 0.840g/cm^2 or femoral neck BMD ≤ 0.600g/cm^2 measured by Hologic apparatus
  OR
  Mean lumbar spine (L2-L4) BMD ≤ 0.949g/cm^2 or femoral neck BMD ≤ 0.743g/cm^2 measured by Lunar apparatus.
- Caucasian, ambulatory males, ≥ 65 years old (with no upper age limit).

Study drug:
S 12911 sachets containing 2 g of active principle. The daily dose was 2 g of active principle administered orally (1 sachet/day in the evening at bedtime).
During the study, all patients received calcium (1000 mg/day) and vitamin D (800 IU/day) supplements taken at lunchtime.

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Reference product: placebo sachets.
The daily dose was 1 sachet/day (in the evening at bedtime).
During the study, all patients received calcium (1000 mg/day) and vitamin D (800 IU/day) supplements taken at lunchtime.

Duration of treatment:
Run-in period (W-2 to M0) with calcium and vitamin D treatment only.
Active treatment period: 24 months.

Criteria for evaluation:
Efficacy measurements
All scans from patients included in the study were centralized for analysis. The Dual-energy X-ray Absorptiometry (DXA) central reading centre determined BMD of each vertebrae between L1 and L4 as well as total hip and femoral neck BMD. All the BMD data measured with a Lunar apparatus were converted in "Hologic" using the standardisation formulae.
Main criterion: lumbar L2-L4 BMD assessed at selection, M6, M12, M18 and M24 visits.
Secondary criteria:

- Femoral neck and total hip BMD assessed at selection, M6, M12, M18 and M24 visits.
- Biochemical Bone Markers: serum CTX I (s-CTX-I), Bone Alkaline Phosphatase (b-ALP), N-terminal propeptide of type I procollagene (PINP), Serum osteocalcin (sOC) were assessed at M0, M3, M6, M12, M18 and M24 visits.
- The quality of life was assessed using 4 items of the Qualiost® questionnaire at inclusion, M6, M12, M18 and M24 visits.

Safety measurements:

- Adverse events at each visit.
- Vital signs (weight, height, systolic and diastolic blood pressure, heart rate) at selection, inclusion, M3, M6, M12, M18 and M24 visits (except height and weight not assessed at inclusion and M3 visits).
- Laboratory safety parameters: biochemistry parameters (Total ALP, bilirubin, ASAT, ALAT, GGT, blood and urine Ca, P and creatinine, Na, K, Cl, protein electrophoresis, CPK (and isoenzymes if CPK above the upper normal range) and haematology parameters (red blood cell count, haemoglobin, haematocrit, MCV, white blood cell (WBC) count and differential WBC count, platelet count).
- Haemostasis parameters (prothrombin time, activated partial prothrombin time, prothrombin activation peptide (F1+F2 fragment), fibrinogen, antithrombin III, protein C, protein S, facteur VIII, homocystein (if increased +folic acid and vitamin B12)) at inclusion for all patients and in a subgroup at post-baseline visits.
- ECG parameters in Canadian patients at inclusion, M6, M12, M18 and M24 visits.
- Assessment of vertebral fractures by X-ray for all patients at selection and M24 visits and in a subgroup by DXA at inclusion and M24 visits.

Drug concentrations:
Serum levels of strontium were assessed by high frequency inductively coupled plasma atomic emission spectrophotometry (ICP-AES) at inclusion, M3, M6, M12, M18 and M24 visits.

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Statistical methods:

Efficacy analysis:

The Full Analysis Set (FAS, main analysis set) included all randomised patients who took at least one dose of the study treatment and having at least one baseline and one post baseline assessable BMD L2-L4 measurement.

Primary efficacy criterion : lumbar L2-L4 BMD

Main analysis:

The L2-L4 BMD was expressed as relative change from baseline to the last available post-baseline value under treatment over 12 months (End). The comparison between S 12911 and placebo was performed in the FAS using a linear model studying treatment effect with country as covariate. Estimate of the difference between adjusted group means and Standard Error of the estimate (SE) were provided with its 95% Confidence Interval (CI) and the associated p-value.

Sensitivity analysis:

- The same analysis was performed in the PPS.
- Treatment groups were compared on the relative change from baseline to End using a general linear model adjusted on risk factors (age, prevalent vertebral fractures).

Secondary analysis (in the FAS and the PPS):

- The same linear model as above was performed on the relative change from baseline to each visit
- The same linear model adjusted on baseline BMD was performed on the change from baseline to End and from baseline to each visit. Descriptive statistics were provided for each visit until M12.

Secondary efficacy criteria : Femoral neck BMD, total hip BMD:

- Femoral neck, total hip BMD: similar analyses were performed as for the main efficacy criterion.
- Bone Markers: Strontium ranelate was compared with placebo in the FAS and the PPS on the relative change between baseline and each visit until M12 (including End). Estimate of the differences between country adjusted means and 95% CI were provided. The same model was used on the change from baseline.
- Quality of life assessment: The four items (Pain in middle/upper part of back, Pain when walking/climbing stairs, Discomfort in the same position, Pain interfered with patient sleep) were described as the change from baseline to End in classes: improvement, no change, worsening in the FAS and in the PPS. The treatment groups were compared on the change of Quality of life mean score from baseline to End and to each visit until M12 using a general linear model with country (random effect) and baseline (fixed effect) as covariates. Estimate of the difference between adjusted group means and SE were provided with its 95% CI and the associated p-value.

Safety analysis:

Adverse events, laboratory parameters, vital signs and ECG were assessed through descriptive statistics.

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Overall disposition of patients is summarised below. Patients who prematurely discontinued the study treatment could be maintained in the study.

Overall patients disposition during the study (M0-M12)

Status	**S 12911**	**Placebo**	**All**
	n (%)	n (%)	n (%)
Included (randomised)	**174 (100.0)**	**87 (100.0)**	**261 (100.0)**
In compliance with the protocol	142 (81.6)	70 (80.5)	212 (81.2)
With a protocol deviation before or at inclusion	32 (18.4)	17 (19.5)	49 (18.8)
Withdrawn from treatment due to	***42* (24.1)***	***15 (17.2)***	***57* (21.8)***
Adverse event	24* (13.8)	9 (10.3)	33* (12.6)
Non medical Reason	14 (8.0)	6 (6.9)	20 (7.7)
Protocol deviation	4 (2.3)	-	4 (1.5)
Withdrawn from treatment but remained in the study	*8 (4.6)*	*4 (4.6)*	*12 (4.6)*
Withdrawn from the study due to	**35 (20.1)**	**11 (12.6)**	**46 (17.6)**
Adverse event	19 (10.9)	4 (4.6)	23 (8.8)
Non medical Reason	13 (7.5)	7 (8.0)	20 (7.7)
Protocol deviation	3 (1.7)	-	3 (1.1)
Lost to follow-up	**-**	**-**	**-**
Completed the M12 visit	**139 (79.9)**	**76 (87.4)**	**215 (82.4)**
On study treatment	***131 (75.3)***	***72 (82.8)***	***203 (77.8)***
In compliance with the protocol	127 (73.0)	72 (82.8)	199 (76.2)
With a protocol deviation after inclusion	4 (2.3)	-	4 (1.5)
Without the study treatment	***8 (4.6)***	***4 (4.6)***	***12 (4.6)***
In compliance with the protocol	-	2 (2.3)	2 (0.8)
With a protocol deviation after inclusion	8 (4.6)	2 (2.3)	10 (3.8)

% Percent of the Randomised Set

**not including patient No. 032 250 0302 00041 who never took the study treatment and withdrew from the study at the M3 visit.*

A total of 261 patients were included in the study: 174 patients in the S 12911 group and 87 patients in the placebo group. Of them, 215 patients (82.4%) completed the M12 visit (139 patients in the S 12911 group and 76 patients in the placebo group), of whom 203 patients (77.8%) were still under treatment.

Overall, 49 patients presented 55 protocol deviations at inclusion, 32 patients (18.4%) in the S 12911 group and 17 patients (19.5%) in the placebo group. During the study, 41 patients presented 64 protocol deviations; 31 patients (17.8%) in the S 12911 group, and 10 patients (11.5%) in the placebo group. Most deviations at inclusion and during the study concerned the study management and were similarly distributed among the two treatment groups.

Main baseline characteristics are summarised below.

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SUMMARY – CONCLUSIONS(Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Baseline characteristics in the Randomised Set

Parameter (unit)		S 12911 (N = 174)	Placebo (N = 87)	All (N = 261)
Age (years)	n	174	87	261
	Mean ± SD	73.1 ± 6.1	72.6 ± 5.7	72.9 ± 6.0
	Min - Max	65 - 90	65 - 88	65 - 90
BMI (kg/m²)	n	174	87	261
	Mean ± SD	25.2 ± 3.6	26.0 ± 4.1	25.5 ± 3.7
	Min - Max	15.2 - 36.9	18.8 - 34.9	15.2 - 36.9
Lumbar L2-L4 BMD (g/cm²)	n	170	87	257
BMD (g/cm²)	Mean ± SD	0.819 ± 0.098	0.852 ± 0.137	0.830 ± 0.113
	Min - Max	0.607 - 1.175	0.631 - 1.360	0.607 - 1.360
T-score (Hologic men reference)	Mean ± SD	-2.696 ± 0.888	-2.391 ± 1.242	-2.593 ± 1.030
	Min - Max	-4.620 - 0.544	-4.407 - 2.223	-4.620 - 2.223
At least one prevalent vertebral fracture	n	173	87	260
	n (%)	50 (28.9)	22 (25.3)	72 (27.7)
At least one previous osteoporotic peripheral fracture	n	174	87	261
	n (%)	20 (11.5)	9 (10.3)	29 (11.1)
25(OH) vitamin D3 (nmol/L)	n	169	86	255
	Mean ± SD	64.82 ± 17.9	65.57 ± 19.42	65.07 ± 18.39

Age of randomised patients ranged from 65 to 90 years with a mean ± SD of 72.9 ± 6.0 years. BMI ranged from 15.2 to 36.9 kg/m² with a mean of 25.5 ± 3.7 kg/m². All patients were ambulatory. Current smoking habits was reported by 16 patients (9.2%) in the S 12911 group and 13 patients (14.9%) in the placebo group.

Hypertension was their most frequently reported medical history (41.8%) followed by benign prostatic hyperplasia (26.1%) and hypercholesterolaemia (22.2%). The most frequent treatments at inclusion were antithrombotic agents (32.2%), lipid modifying agents (29.5%) and agents acting on the renin-angiotensin system (29.1%).

All randomised patients presented primary osteoporosis. Mean time since diagnosis was 26.6 ± 48.6 months and more than one third of patients (37.9%) were diagnosed at the selection visit. A total of 84 patients (32.2%) reported at least one previous treatment for osteoporosis, mainly mineral supplements (calcium) (22.6%), vitamins (12.3%) and biphosphonates (11.5%).

Among randomised patients, 11.1% reported at least one previous osteoporosis-related peripheral fracture and 27.7% at least one prevalent vertebral fracture.

The mean baseline lumbar L2-L4 BMD was 0.830 ± 0.113 g/cm², the mean baseline femoral neck BMD was 0.622 ± 0.086 g/cm² and the mean baseline total hip BMD was 0.790 ± 0.114 g/cm².

Global compliance was satisfactory (mean ± SD of 91.7 ± 12.5% in the FAS) and was similar in the two groups.

Mean blood strontium levels reached the steady state at the M3 visit. At the M12 visit, mean blood level in the S 12911 group was [redacted] in the Safety Set.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Primary assessment criterion: lumbar L2-L4 BMD in the FAS

Relative changes from baseline to last value (End) in the FAS (main analysis)

After one year of treatment, the relative change from baseline to End in L2-L4 BMD was 7.1 ± 6.0% in the S 12911 group and 1.7 ± 4.4% in the placebo group, with a statistically significant difference between groups (E (SE) = 5.3 (0. 8); 95%CI = [3.86 ; 6.79]; p < 0.001). This result was confirmed by the sensitivity analysis adjusted for risk factors (age, prevalent vertebral fractures): E (SE) = 5.3 (0.8), 95% CI [3.86 ; 6.80], p < 0.001.

Lumbar L2-L4 BMD relative changes (%) from baseline to End in the FAS (N = 243)

Lumbar L2-L4 BMD (g/cm²)		**S 12911 (N = 161)**	**Placebo (N = 82)**
Baseline	Mean ± SD	0.820 ± 0.098	0.847 ± 0.136
	Min - Max	0.607 - 1.175	0.631 - 1.360
End	Mean ± SD	0.876 ± 0.106	0.860 ± 0.132
	Min - Max	0.632 - 1.230	0.641 - 1.364
Relative changes from baseline to End (%)	**Mean ± SD**	**7.05 ± 6.00**	**1.72 ± 4.44**
	Min - Max	-10.46 - 30.32	-17.39 - 15.54
Statistical analysis	E (SE)(1)	5.32 (0.75)	
	95%CI(2)	[3.86 ; 6.79]	
	p-value(3)	**< 0.001**	

Baseline value at selection visit, End last value on treatment

(1) Estimate (Standard Error) of adjusted means difference S 12911-placebo (country as random effect)

(2) 95% Confidence Interval of the estimate

(3) Corresponding p-value (Student t-test, general linear model).

These results were confirmed in the PPS (defined as patients from the FAS with sufficient treatment exposure and no deviations affecting main study efficacy criteria). The mean relative increase in L2-L4 BMD from baseline to M12 was 8.32 ± 5.95% in the S 12911 group *versus* 1.57 ± 4.36% in the placebo group. The estimate of the between-group difference was E (SE) = 6.8 (0.8), 95%CI [5.12 ; 8.39], p < 0.001. This result was confirmed by the sensitivity analysis adjusted for risk factors (age, prevalent vertebral fractures): E (SE) = 6.8 (0.8), 95% CI [5.16 ; 8.45], p < 0.001.

Relative changes from baseline to each visit

In the S 12911 group, the mean relative increases from baseline in L2-L4 BMD were 4.61 ± 4.56% at M6 and 8.18 ± 5.92% at M12. During the same periods, an increase of low magnitude was observed in the placebo group with a relative change from baseline to M6 of 0.52 ± 4.36% and from baseline to M12 of 1.79 ± 4.55%. The difference between groups in relative changes was statistically significant both at M6 (E(S E) = 4.09 (0.63)%; 95%CI = [2.85 ; 5.33], p < 0. 001) and at M12 (E (S E) = 6.38 (0. 81), 95% CI = [4.78 ; 7.98], p < 0.001).

Changes from baseline to each visit and to End

At both visits and at last evaluation (End), the between-group differences in changes from baseline were significant:

- M6: E (SE) = 0.03 (0.01) g/cm², 95%CI = [0.02 ; 0.04], p < 0.001.
- M12: E (SE) = 0.05 (0.01) g/cm², 95%CI = [0.04 ; 0.06], p < 0.001.
- End: E (SE) = 0.04 (0.01) g/cm², 95%CI = [0.03 ; 0.05], p < 0.001.

All results were confirmed in the PPS.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Secondary criteria:

Femoral neck BMD

In the FAS, the femoral neck BMD increased from baseline to End in the S 12911 group, whereas it remained stable in the placebo group. The relative changes from baseline to End were 3.12 ± 4.63% in the S 12911 and 0.22 ± 4.05% in the placebo group. The difference between groups in relative changes was statistically significant ($p < 0.001$). All results were confirmed in the PPS

Femoral neck BMD relatives changes from baseline to end (%) in the FAS (N = 243)

BMD		**S 12911 (N = 161)**	**Placebo (N = 82)**
Baseline (g/cm²)	Mean ± SD	0.629 ± 0.082	0.629 ± 0.092
	Min - Max	0.435 - 0.892	0.470 - 0.871
End (g/cm²)	Mean ± SD	0.648 ± 0.084	0.630 ± 0.097
	Min - Max	0.445 - 0.909	0.419 - 0.944
Relative change from baseline to End (%)	Mean ± SD	**3.12 ± 4.63**	**0.22 ± 4.05**
	Min - Max	-9.06 - 34.98	-10.76 - 11.49
Statistical analysis	E (SE)[1]	2.90 (0.62)	
	95%CI[2]	[1.67 ; 4.12]	
	p-value[3]	**< 0.001**	

Baseline value at selection visit, End last value on treatment

(1) Estimate (Standard Error) of adjusted means differences S 12911 – Placebo (country as random effect)

(2) 95% Confidence interval of the estimate

(3) Corresponding p-value (Student t-test, general linear model)

Total hip BMD

In the FAS, the total hip BMD increased from baseline to End in the S 12911 whereas it remained stable in the placebo group. The relative changes from baseline to end were 2.42 ± 4.89% in the S 12911 group and 0.49 ± 2.47% in the placebo group, and were significantly different ($p < 0.001$). All results were confirmed in the PPS.

Total hip BMD relative changes from baseline to end (%) in the FAS (N = 243)

BMD		**S 12911 (N = 161)**	**Placebo (N = 82)**
Baseline (g/cm²)	Mean ± SD	0.793 ± 0.113	0.798 ± 0.117
	Min - Max	0.335 - 1.075	0.551 - 1.107
End (g/cm²)	Mean ± SD	0.810 ± 0.111	0.801 ± 0.116
	Min - Max	0.460 - 1.113	0.550 - 1.147
Relative change from baseline to End (%)	**Mean ± SD**	**2.42 ± 4.89**	**0.49 ± 2.47**
	Min - Max	-23.74 - 37.52	-7.41 - 5.61
Statistical analysis	E (SE)[1]	1.96 (0.58)	
	95%CI[2]	[0.81 ; 3.11]	
	p-value[3]	**< 0.001**	

Baseline value at selection visit, End last value on treatment

(1) Estimate (Standard Error) of adjusted means difference S 12911 – Placebo (country as random effect)

(2) 95% Confidence interval of the estimate

(3) Corresponding p-value (Student t-test, general linear model)

Bone markers

Mean serum CTX, a marker of bone resorption, decreased in the S 12911 group by -4.14 ± 50.39% while it increased in the placebo group by 21.74 ± 68.27%. The estimate of the adjusted means differences S12911-Placebo was -25.88 (7.86)% and the between-group difference was statically significant ($p = 0.001$). The mean b-ALP (a marker for bone formation) levels were elevated at baseline and tended to decrease in both groups from baseline to End. The decrease was less marked in the S 12911 group (-1.69%) than in the placebo group (-6.07%). The estimate of adjusted means differences S12911-Placebo was 4.46 (2.96)% without statistically significance.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Quality of life

Quality of life was evaluated by assessing particularly back pain (4 items of the Qualiost® questionnaire). An improvement (*i.e.* a score decrease) in both groups from baseline to End was observed, with a more marked improvement in the S 12911 group (-0.16 ± 0.64 *versus* -0.07 ± 0.48 in the placebo group).

These results indicate an improvement in patients treated with S 12911 as compared to placebo in particular regarding the "pain interfering with patient sleep", improved in 16.2% of the patients of the S 12911 group *versus* 5.1% in the placebo group. Unplanned analyses showed that the between-group difference was statistically significant (p = 0.016).

SAFETY RESULTS

Safety results are summarised in the table below:

Main safety results

		S 12911 (N = 173)	**Placebo (N = 87)**
At least one emergent adverse event	**n (%)**	**138 (79.8)**	**77 (88.5)**
At least one treatment-related emergent adverse event	**n (%)**	**40 (23.1)**	**23 (26.4)**
At least one emergent adverse event leading to treatment discontinuation	**n (%)**	**22 (12.7)**	**8 (9.2)**
At least one serious emergent adverse event	**n (%)**	**31 (17.9)**	**13 (14.9)**
Treatment-related serious emergent adverse event	n (%)	4 (2.3)	1 (1.1)
Deaths	**n (%)**	**2 (1.2)**	**1 (1.1)**
Biological investigations			
At least one emergent blood calcium value < lower limit of reference range	n (%)*	52 (33.1)	4 (4.9)
At least one emergent blood phosphorus value > upper limit of reference range	n (%)*	22 (14.0)	1 (1.2)

** Percent calculated with respect to total number of assessable patients*

The overall frequency of patients who reported at least one **emergent adverse event** was slightly lower in the S 12911 group than in the placebo group: 138 patients (79.8% of patients) in the S 12911 group and 77 patients (88.5% of patients) in the placebo group.

The most frequently affected system organ classes were gastrointestinal disorders (23.7% in the S 12911 group *versus* 24.1% in the placebo group), musculoskeletal and connective tissue disorders (22.0% and 29.9%, respectively) and infections and infestations (22.0% and 24.1%, respectively). Most system organ classes were affected at comparable incidence in both groups or with a lower incidence in the S 12911 group, except investigations, more frequently reported in the S 12911 group (11.0%) than in the placebo group (5.7%). In the S 12911 group, the most commonly reported emergent adverse event were hypertension (8.1% *versus* 5.7% in the placebo group), back pain (5.8% and 5.7%, respectively) and arthralgia (4.6% and 3.4%, respectively).

As regards expected drug reactions with S 12911, the incidences were in accordance with the current knowledge on the S 12911 safety profile.

Most emergent adverse events were graded as mild or moderate (95.6% of the events). **Severe emergent adverse events** occurred in 15 patients (8.7%) in the S 12911 group and 10 patients (11.5%) in the placebo group. No between-groups difference was detected as regards the nature and the frequency of these severe events.

Treatment-related emergent adverse events were reported in 63 patients: 40 patients (23.1%) in the S 12911 group and 23 patients (26.4%) in the placebo group. The system organ classes most commonly affected were gastrointestinal disorders (6.4% of the patients in the S 12911 group *versus* 11.5% in the placebo group) and skin subcutaneous disorders (6.9% *versus* 3.4%, respectively).

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Premature discontinuation of treatment due to adverse events affected 22 patients (12.7%) in the S 12911 group and 8 patients (9.2%) in the placebo group. Events responsible for treatment withdrawal concerned mainly gastrointestinal disorders (3.5% *versus* 3.4%, respectively) and skin and subcutaneous disorders (4.0% *versus* 1.1%, respectively). Among skin and subcutaneous disorders, toxic skin eruption was the only preferred term reported more than once (2 cases in the S 12911 group). Two cases of serious deep vein thrombosis, considered treatment-related by the investigator, led to treatment withdrawal. Both were improved at the end of the one-year period.

Emergent serious adverse event were reported in 44 patients: 31 patients (17.9%) in the S 12911 group and 13 patients (14.9%) in the placebo group. The most frequently affected system organ classes were cardiac disorders (in 3.5% of the patients in the S 12911 group *versus* 4.6% in the placebo group) and neoplasms (2.3% and 1.1%, respectively). The serious adverse events spanned 15 different system organ classes and therefore did not display any meaningful trend. In the S 12911 group, the preferred terms reported twice were angina pectoris, prostate cancer, deep vein thrombosis and iron deficiency anaemia.
Three patients died during the one-year period of treatment: 2 patients (1.2%) in the S 12911 group, one from sudden death and one from unknown cause and one patient (1.1%) in the placebo group from cerebral haemorrhage. The three patients who died during the study had history of cardiovascular diseases and deaths were considered unrelated to the study treatment according to the investigator.

Laboratory tests

Mean blood creatinine increased over the one-year follow-up, more markedly in the S 12911 group than in the placebo group (5.2 ± 9.6 µmol/L *versus* 1.5 ± 13.9 µmol/L), but no emergent potentially clinically significant value was reported.
Mean CPK level increased in the S 12911 group from baseline to last value (+20.4 ± 51.5 IU/L), whereas it remained stable in the placebo group (0.7 ± 51.3 IU/L). In the S 12911 group, 6 patients (3.8%) had an emergent high out-of-reference range CPK value as compared to 4 patients (4.9%) in the placebo group. No potentially clinically significant CPK value, *i.e.* no values > 3 ULN (Upper Limit of the Normal range), was reported in any treatment group.
Neither clinically relevant changes, nor differences between groups were detected for haematological parameters.

Vital signs (weight, height, blood pressure and heart rate)

No clinically relevant changes over time or differences between groups were detected.

Electrocardiogram (in Canadian patients)

No clinically relevant changes over time or differences between groups were detected. No emergent ECG abnormality was reported in the S 12911 group over the one-year follow-up.

Phosphocalcic homoeostasis parameters

As observed in previous studies, a decrease in blood calcium and an increase in blood phosphorus were observed, of too small amplitude to have clinical relevance. This effect was probably related to the mechanism of action of S 12911, which is a full agonist of calcium sensing receptor.

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CONCLUSION

This study aimed at confirming in men the results of the pivotal phase III studies with strontium ranelate in women. The baseline characteristics of the patients were in keeping with the target population defined in the protocol and representative of the osteoporotic male population. Compliance and exposure to treatment were satisfactory. Serum strontium levels in treated patients reached the same levels as in previous phase III studies in women.

A marked increase in the mean lumbar L2-L4 bone mineral density (main efficacy criterion) was observed as compared to placebo. The magnitude of the effect was consistent with expected results based on the large SOTI/TROPOS Phase III studies conducted in osteoporotic women, where a clear relationship between the increase in BMD and antifracture efficacy was shown. Similar antifracture efficacy of S 12911 may thus be expected in osteoporotic men.

Safety results did not reveal any unexpected adverse events in men exposed to S 12911.

Date of the report: 17 December 2010