Document title	**Clinical Study Report Synopsis**
Study title	**The efficacy and safety of 2g 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** **Second Report M0-M24 analysis**
Study drug	**Strontium ranelate (S 12911)**
Studied indication	**Male osteoporosis**
Development phase	**Phase III**
Protocol code	**CL3-12911-032-EXT**
Study initiation date	**11 December 2007**
Study completion date	**04 March 2011**
Main coordinator	[redacted] **Belgium**
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France** **Servier Canada Inc.** **235 Armand-Frappier Blvd** **Laval, Quebec Canada H7V4A7** **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 15 March 2012** **Previous report: MALEO NP29799 (M0-M12)**

~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex - 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 2g 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
Protocol No.: CL3-12911-032
Second Report: M0-M24 analysis
(The first report, over the period 0 – 12 months corresponds to the main analysis)

International Coordinator: [redacted] Belgium.

Study centres: (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), Russia (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: 04 March 2011	**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 (Internal Report NP29799).
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 over 2 years (results are presented in this specific report)

Methodology:
Multicentre, 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 similar to those of postmenopausal women included in previous phase III studies SOTI and TROPOS:
  Mean lumbar spine (L2-L4 BMD) $\leq$ 0.840 g/cm² or femoral neck BMD $\leq$ 0.600 g/cm² measured by Hologic apparatus,
  OR
  Mean lumbar spine (L2-L4 BMD) $\leq$ 0.949 g/cm² or femoral neck BMD $\leq$ 0.743 g/cm² measured by Lunar apparatus.
- Caucasian, ambulatory males, $\geq$ 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, except those with hypercalciuria (> 4mg/kg/24h) received supplements of calcium (1000 mg/day) and vitamin D (800 IU/day), taken at lunchtime.

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Reference product: matching placebo sachets
The daily dose was 1 sachet/day (in the evening at bedtime).
During the study, all patients, except those with hypercalciuria (> 4mg/kg/24h) received supplements of calcium (1000 mg/day) and vitamin D (800 IU/day), taken at lunchtime.

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

Criteria for evaluation:

Efficacy measurements
All scans from patients included in the study were centralised for analysis. The Dual-energy X-ray Absorptiometry (DXA) central reading centre determined BMD of each vertebra from L1 to L4 as well as total hip and femoral neck BMD. All the BMD data measured with a Lunar apparatus were converted in "Hologic" using a standardisation formula. The cross-calibration done at M24 slightly modified the calibration factor for each investigational centre, over that which had been applied for the period [M0-M12], thus changing the corrected and calibrated BMD values previously reported. All values were therefore affected, but the net change over the period [M0-M12] was not significantly affected. The baseline values in the RS presented in the 1 year report were: 0.819 ± 0.098 g/cm² in the S 12911 *versus* 0.852 ± 0.137 in the placebo group; the Hologic T-scores were -2.70 ± 0.89 *versus* -2.39 ± 1.24, respectively.

The main criterion was 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 (sCTX-I), Bone Alkaline Phosphatase (bALP), N-terminal propeptide of type I procollagen (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, M18 and M24 visits.

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Criteria for evaluation (Cont'd):

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 alkaline phosphatase, bilirubin, ASAT, ALAT, GGT, blood and urine calcium, phosphorus and creatinine, sodium, potassium, chloride, protein electrophoresis, creatinine phosphokinase (CPK) and isozymes if CPK above the upper normal range), and haematological parameters (red blood cell count, haemoglobin, haematocrit, mean corpuscular volume (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, factor VIII, homocysteine (if increased + folic acid and vitamin B12)) at inclusion for all patients and in a subgroup at post-baseline visits.
- ECG parameters in patients recruited in Canada at inclusion, M6, M12, M18 and M24 visits.
- Assessment of vertebral fractures by X-ray for all patients at selection and M24 visit (or withdrawal visit) and by DXA technique in a subset of patients at inclusion and M24.

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.

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 measurements. Efficacy parameters were analysed in the FAS (no PPS was defined for the 2-year analyses).

Primary efficacy criterion: lumbar L2-L4 BMD

Main analysis:

The L2-L4 BMD was expressed as relative change from baseline to End (End = the last available post-baseline value under treatment or the first available post-baseline value in case of no post-baseline value measured under treatment). The comparison between S 12911 and placebo was performed 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:

- Treatment groups were compared on the relative change from baseline to End using a general linear model adjusted on country and risk factors (age, prevalent vertebral fractures).

Secondary analysis

- The same linear models as above were performed on the relative change from baseline to each visit.
- A linear model studying treatment effect with country and baseline BMD as covariates was performed on the absolute change from baseline to End and from baseline to each visit.

Descriptive statistics were provided for each visit.

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Statistical methods (Cont'd):

Secondary efficacy criteria: femoral neck BMD, total hip BMD

- Femoral neck, total hip BMD: similar analyses except the sensitivity analysis were performed as for the main efficacy criterion.
- Bone markers: strontium ranelate was compared with placebo on the relative change between baseline and each visit (including End). Estimate of the difference between country-adjusted means, standard error (SE) and 95% CI using a general linear model were provided. A linear model studying treatment effect with country and baseline BMD as covariates was performed on the change from baseline to End and from baseline to each visit.
- Quality of life assessment: the four items of the Qualiost® (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. The treatment groups were compared on the change of quality of life mean score from baseline to End and to each visit using a general linear model with country and baseline as covariates. Estimate of the difference between adjusted-group means and SE were provided with its 95% CI and the associated p-value.

Safety analyses:

- Adverse events, laboratory parameters, vital signs, ECG and vertebral fractures were assessed through descriptive statistics. (The DXA data on vertebral fractures was not exploitable).

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

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

Disposition of patients in the Randomised Set

Status	**S 12911**	**Placebo**	**All**
	n (%)	n (%)	n (%)
Included and randomised	**174 (100)**	**87 (100)**	**261 (100)**
In compliance with the protocol	141 (81.0)	69 (79.3)	210 (80.5)
With a protocol deviation before or at inclusion	33 (19.0)	18 (20.7)	51 (19.5)
Withdrawn from treatment due to	**56 (32.2)**	**24 (27.6)**	**80 (30.7)**
Adverse event	33 (19.0)	13 (14.9)	46 (17.6)
Non-medical reason	19 (10.9)	11 (12.6)	30 (11.5)
Protocol deviation	4 (2.3)	-	4 (1.5)
Lost to follow-up	**-**	**-**	**-**
Completed the study	**127 (73.0)**	**71 (81.6)**	**198 (75.9)**
On study treatment	117 (67.2)	63 (72.4)	180 (69.0)
Without the study treatment	10 (5.7)	8 (9.2)	18 (6.9)
FAS	**161 (92.5)**	**82 (94.3)**	**243 (93.1)**
Safety Set	**173 (99.4)**	**87 (100)**	**260 (99.6)**

n Number of patients concerned; % Percent of the Randomised Set

A total of 261 patients were included in the study: 174 patients were randomised to the S 12911 group and 87 patients were randomised to the placebo group. Of them, 198 patients (75.9%) completed the M24 visit (127 patients in the S 12911 group and 71 patients in the placebo group), of whom 180 (69.0%) were still under treatment. Premature discontinuation of study treatment over the 2 years concerned 32.2% of patients in the S 12911 group *versus* 27.6% in the placebo group and the main reason for stopping was an adverse event (19.0% *versus* 14.9%, respectively).

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SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Overall, 51 patients presented 60 protocol deviations at inclusion, 33 patients (19.0%) in the S 12911 group and 18 patients (20.7%) in the placebo group. During the study, 60 patients presented 96 protocol deviations: 42 patients (24.1%) in the S 12911 group, and 18 patients (20.7%) 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.

The main baseline characteristics are summarised in the table below.

Patients of the Randomised Set were aged from 65 to 90 years with a mean ± SD of 72.9 ± 6.0 years. The overall mean BMI was 25.5 ± 3.7 kg/m²; 43.3% of patients were overweight.

The mean baseline lumbar L2-L4 BMD (overall) was 0.817 ± 0.112 g/cm², the mean baseline femoral neck BMD was 0.613 ± 0.090 g/cm² and the mean baseline total hip BMD was 0.779 ± 0.119 g/cm².

The most frequently reported medical histories were hypertension (43.1% of patients in the S 12911 group, *versus* 39.1% in the placebo group), benign prostatic hyperplasia (28.2% *versus* 23.0%, respectively) and hypercholesterolaemia (21.3% *versus* 24.1%, respectively). More frequent in the S 12911 group than in the placebo group were an antecedent of hypertension, myocardial ischaemia (10.3% *versus* 3.4%, respectively) and inguinal hernia (17.8% *versus* 8.0%, respectively); at the HLGT level, a history of coronary artery disorder was reported in 20.7% *versus* 16.1%, respectively.

Baseline characteristics in the Randomised Set

Parameter (unit)		**S 12911 (N = 174)**	**Placebo (N = 87)**	**All (N = 261)**
Age (years)	Mean ± SD	73.1 ± 6.1	72.6 ± 5.7	72.9 ± 6.0
	Min ; Max	65 ; 90	65 ; 88	65 ; 90
BMI (kg/m^2)	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	n	170	87	257
BMD (g/cm^2)	Mean ± SD	0.806 ± 0.097	0.838 ± 0.134	0.817 ± 0.112
	Min ; Max	0.608 ; 1.175	0.610 ; 1.360	0.608 ; 1.360
T-score (Hologic men)	Mean ± SD	-2.82 ± 0.88	-2.52 ± 1.22	-2.72 ± 1.02
	Min ; Max	-4.61 ; 0.55	-4.60 ; 2.22	-4.61 ; 2.22
Prevalent vertebral fracture	n (%)	53 (30.6)	22 (25.3)	75 (28.9)
Previous osteoporotic peripheral fracture	n (%)	20 (11.5)	9 (10.3)	29 (11.1)
25(OH) vitamin D3 (nmol/L)	n	170	86	-
	Mean ± SD	62.2 ± 17.2	62.8 ± 18.6	-

n Number of patients concerned; % Percent of the Randomised Set

Note The differences in the baseline values from those presented in the year 1 report were due to the cross-calibration procedure of the DXA scans (see efficacy measurements)

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SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

At least one previous treatment for osteoporosis was reported by 32.2%, which were mainly (22.6%) mineral supplements (calcium), vitamins (12.3%) and biphosphonates (11.5%).
The most frequent treatments other than antiosteoporotics at inclusion were, antithrombotic agents (mainly aspirin; 34.5% *versus* 26.4%), lipid-modifying agents (31.6% *versus* 26.4%) and agents acting on the renin-angiotensin system (32.2% *versus* 23.0%) and beta-blocking agents (22.4% *versus* 16.1%). Thus, it may be noted that there were relatively higher use rates of these non-antiosteoporotic treatments in the S 12911 group.
All patients presented with primary osteoporosis, for which more than one third of patients (37.9%) were diagnosed at the selection visit. The mean time since diagnosis was 26.6 ± 48.6 months.

The mean duration of treatment was slightly shorter in the S 12911 group than in the placebo group (568.1 ± 264.6 *versus* 616.9 ± 229.7 days; i.e. 18.7 ± 8.7 months *versus* 20.3 ± 7.6 months). The majority of patients (65.4%) had a treatment exposure between 23 and 25 months. The mean global compliance up to M24 was 91.2 ± 13.7% and of satisfactory level (between 80% and 120%) in 84.6% patients.
Blood strontium levels had reached a steady state in the S 12911 group by the time of the M3 sampling and was maintained until M24. At the M24 visit, the mean strontium level was [redacted] (Safety Set).

In the FAS, the baseline characteristics were similar those described in the RS. The slight imbalances between the groups already described in the RS concerning medical history and concomitant treatments, were also noted in the FAS. The treatment groups were otherwise similar.

EFFICACY RESULTS

Primary assessment criterion: lumbar L2-L4 BMD

Relative changes from baseline to End (the last post-baseline value under treatment until M24 or the first available post-baseline value in case of no post-baseline value measured under treatment): main analysis

Over the 2-year period, the relative change from baseline to End in L2-L4 BMD was 9.7 ± 7.5% in the S 12911 group *versus* 2.0 ± 5.5% in the placebo group, which resulted in a statistically significant between-group difference in favour of S 12911: E (SE) = 7.7 (0.9)%; 95%CI = [5.9 ; 9.5]; p < 0.001. This result was confirmed by the sensitivity analysis adjusted for risk factors (age and prevalent vertebral fractures): E (SE) = 7.6 (0.9)%, 95% CI [5.8 ; 9.5], p < 0.001.

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

Lumbar L2-L4 BMD (g/cm^2)		**S 12911 (N = 161)**	**Placebo (N = 82)**
Baseline	Mean ± SD	0.807 ± 0.098	0.833 ± 0.133
	Min ; Max	0.608 ; 1.175	0.610 ; 1.360
End	Mean ± SD	0.883 ± 0.115	0.846 ± 0.121
	Min ; Max	0.662 ; 1.230	0.656 ; 1.351
Relative changes from baseline to End (%)	Mean ± SD	9.69 ± 7.52	1.98 ± 5.48
	Min ; Max	-10.79 ; 35.44	-17.54 ; 15.69
Statistical analysis	E (SE)[(1)]	7.71 (0.93)	
	95%CI[(2)]	[5.88 ; 9.54]	
	p-value[(3)]	**< 0.001**	

Baseline value at selection visit
(1) Estimate (Standard Error) of adjusted means difference S 12911-placebo (country as random effect) using a general linear model
(2) 95% Confidence Interval of the estimate
(3) Corresponding p-value (Student t-test, general linear model)
Note The differences in the baseline values from those presented in the year 1 report were due to the cross-calibration procedure of the DXA scans (see efficacy measurements)

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Relative changes from baseline to values under treatment at each visit

In the S 12911 group, the mean relative increases from baseline in L2-L4 BMD were 4.6 ± 4.6% at M6 (n = 144), 8.2 ± 5.9% at M12 (n = 129), 10.2 ± 6.3% at M18 (n = 115) and 11.9 ± 7.0% at M24 (n = 112). During the same periods, an increase of low magnitude was observed in the placebo group with a relative change from baseline to M12 of 1.9 ± 4.6% (n = 72), from baseline to M18 of 1.2 ± 4.5% (n = 68) and from baseline to M24 of 2.1 ± 5.6% (n = 60).

The difference between groups on the relative change for all periods of 12 months or more, showed a statistically significant result in favour of S 12911:

- From baseline to M12: E = 6.2%, 95% CI = [4.6 ; 7.8], p < 0.001.
- From baseline to M18: E = 9.0%, 95% CI = [7.2 ; 10.7], p < 0.001.
- From baseline to M24: E = 9.8%, 95% CI = [7.8 ; 11.9], p < 0.001).

Absolute changes from baseline to values under treatment at each visit and to End

At all the visits and at End, the between-group differences in absolute changes from baseline were statistically significantly in favour of S 12911.

- From baseline to M12: E = 0.05 g/cm², 95% CI = [0.04 ; 0.06], p < 0.001.
- From baseline to M18: E = 0.07 g/cm², 95% CI = [0.06 ; 0.09], p < 0.001.
- From baseline to M24: E = 0.08 g/cm², 95% CI = [0.06 ; 0.10], p < 0.001.
- From baseline to End: E = 0.06 g/cm², 95% CI = [0.05 ; 0.08], p < 0.001.

Secondary criteria: Femoral neck BMD

The mean femoral neck BMD increased from baseline to End by 3.8 ± 5.2% in the S 12911 group (n = 153) and by 1.0 ± 5.5% in the placebo group (n = 77) (see table below).

Both absolute and relative changes from baseline to End were statistically significantly in favour of S 12911 as compared to placebo (p < 0.001) with an estimated between-group difference of 0.02 g/cm^2 (95% CI [0.01 ; 0.03]) for the absolute change. The estimated between-group difference in relative change was 2.8% (95% CI [1.3 ; 4.2]).

Femoral neck BMD - Relative changes from baseline to End (%) in the FAS (N = 243)

		S 12911 (N = 161)	**Placebo (N = 82)**
	n	153	77
Baseline (g/cm^2)	Mean ± SD	0.620 ± 0.084	0.620 ± 0.095
	Min ; Max	0.428 ; 0.892	0.462 ; 0.872
End (g/cm^2)	Mean ± SD	0.643 ± 0.089	0.626 ± 0.106
	Min ; Max	0.427 ; 0.894	0.431 ; 1.024
Relative changes from baseline to End (%)	Mean ± SD	3.75 ± 5.20	0.99 ± 5.46
	Min ; Max	-9.92 ; 32.01	-11.39 ; 24.81
Statistical analysis	E(SE)[(1)]	2.77 (0.74)	
	95%CI[(2)]	[1.31 ; 4.23]	
	p-value[(3)]	**< 0.001**	

(1) Estimate (Standard Error) of adjusted means difference S 12911 – Placebo (country as random effect) using a general linear model; (2) 95% Confidence interval of the estimate; (3) Corresponding p-value (Student t-test, general linear model)

Note The differences in the baseline values from those presented in the year 1 report were due to the cross-calibration procedure of the DXA scans (see efficacy measurements)

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Secondary criteria (Cont'd):

The differences between groups in relative (and absolute) changes were statistically significantly in favour of S 12911 from baseline to M12, to M18 and to M24 (under treatment). The relative increase from baseline to M24, was 4.4 ± 5.4% in the S 12911 group (n = 104) *versus* 1.1 ± 5.7% in the placebo group (n = 58) with a between-group difference of 3.3% (95% CI = [1.5 ; 5.1], p < 0.001).

Total hip BMD

The mean total hip BMD increased from baseline to End by 3.2 ± 5.1% in the S 12911 group whereas it remained stable in the placebo group (0.0 ± 4.2%).

Both absolute and relative changes from baseline to End were statistically significantly in favour of S 12911 as compared to placebo (p < 0.001) with an estimated between-group difference of 0.02 g/cm^2 (95% CI [0.01 ; 0.03]) for the absolute change and 3.1% (95% CI [1.8 ; 4. 5]) for the relative change.

Total hip BMD - Relative changes from baseline to End (%) in the FAS (N = 243)

Total Hip BMD		**S 12911 (N = 161)**	**Placebo (N = 82)**
	n	153	77
Baseline (g/cm^2)	Mean ± SD	0.782 ± 0.116	0.787 ± 0.121
	Min ; Max	0.336 ; 1.075	0.553 ; 1.107
End (g/cm^2)	Mean ± SD	0.805 ± 0.116	0.787 ± 0.122
	Min ; Max	0.469 ; 1.109	0.510 ; 1.177
Relative changes from baseline to End (%)	Mean ± SD	3.16 ± 5.11	0.02 ± 4.18
	Min ; Max	-6.34 ; 39.58	-8.24 ; 16.23
Statistical analysis	E(SE)[(1)]	3.14 (0.67)	
	95%CI[(2)]	[1.82 ; 4.45]	
	p-value[(3)]	**< 0.001**	

(1) Estimate (Standard Error) of adjusted means difference S 12911 – Placebo (country as random effect) using a general linear model; (2) 95% Confidence interval of the estimate; (3) Corresponding p-value (Student t-test, general linear model)

Note The differences in the baseline values from those presented in the year 1 report were due to the cross-calibration procedure of the DXA scans (see efficacy measurements)

The differences between groups in relative (and absolute) changes were statistically significantly in favour of S 12911 from baseline to M6, to M12, to M18 and to M24 (under treatment). The relative increase from baseline to M24, was 3.7 ± 5.5% in the S 12911 group (n = 104) *versus* 0.1 ± 4.3% in the placebo group (n = 58) with a between-group difference of 3.7% (95% CI = [2.0 ; 5.3], p < 0.001).

Bone markers

Mean sCTX-I concentration (marker of bone resorption) remained fairly stable over the period baseline to End in the S 12911 group (10.7 ± 58.0%, median = 0.0%), whereas it increased in the placebo group (34.9 ± 65.8%, median = 20.0%). The estimate of the between-group difference was -24.1% (95% CI [-40.5 ; -7.8]). This result suggests that there was a decline in bone resorption in the S 12911 group in comparison with placebo. The relative increase of bALP (marker of bone formation) between baseline and End was more marked in the S 12911 group (6.4%) than in the placebo group (1.9%). The estimate of adjusted means difference (S 12911-placebo) was 4.5% (95% CI [-2.9 ; 11.9]).

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Quality of life

Quality of life was evaluated by assessing 4 items of the Qualiost® questionnaire (mainly back pain), in which a decreased score corresponds to an improvement. The mean score decreased in both groups from baseline to End, with a more marked decrease in the S 12911 group (-0.26 ± 0.71 *versus* -0.05 ± 0.54 in the placebo group), the between-group difference was close to the statistical significance (E = -0.13, 95%CI [-0.27 ; 0.01]). The positive tendency that was observed at the M12 cut-off was confirmed over 24 months, with a between-group difference over baseline to M24 that was statistically significant (E = -0.19, 95% CI [-0.33 ; -0.05], p = 0.009 (complementary test)) (n = 107 patients in the S 12911 group et 58 in the placebo group).

Each of the 4 items was more frequently improved in the S 12911 group than in the placebo group, from baseline to End. The largest between-group difference was for the item "pain interfered with patient sleep", improved in 16.8% of the patients of the S 12911 group *versus* 3.9% in the placebo group (p = 0.019, Cochran-Mantel-Haenszel test, complementary analysis).

SAFETY RESULTS

The safety results are summarised in the table below.

The overall frequency of patients who reported at least one **emergent adverse event** was lower in the S 12911 group than in the placebo group: 88.4% of patients *versus* 96.6%, respectively.

Summary of safety results during the treatment period

		S 12911 (N = 173)	**Placebo (N = 87)**
At least one emergent adverse event	n (%)	153 (88.4)	84 (96.6)
At least one treatment-related emergent adverse event	n (%)	50 (28.9)	26 (29.9)
At least one emergent adverse event leading to premature treatment discontinuation	n (%)	31 (17.9)	12 (13.8)
At least one serious emergent adverse event (including death)	n (%)	51 (29.5)	26 (29.9)
Treatment-related serious emergent adverse event	n (%)	6 (3.5)	2 (2.3)
Deaths	n (%)	3 (1.7)	1 (1.1)
Biological investigations			
At least one emergent blood calcium value < lower limit of reference range	n (%)*	56 (35.7)	5 (6.2)
At least one emergent blood phosphorus value > upper limit of reference range	n (%)*	23 (14.7)	2 (2.5)

N Number of patients in treatment group; n number of patients affected; % = (n/N) x 100

** % = (n/ total number of assessable patients) x 100*

The most frequently affected system organ classes (SOCs) in both groups were *musculoskeletal and connective tissue disorders* with a lower frequency of patients affected in the S 12911 group than in the placebo group (30.1% *versus* 39.1%, respectively), *gastrointestinal disorders* (30.1% *versus* 29.9%, respectively) and *infections and infestations* with a lower frequency of patients affected in the S 12911 group than in the placebo group (29.5% *versus* 35.6%, respectively).

More frequently reported in the S 12911 group than in the placebo group were the following SOCs:

- *Cardiac disorders*: 16.2% *versus* 13.8%, respectively, the difference being mainly due to angina pectoris (4.0% *versus* none, respectively) and coronary artery disease (3.5% *versus* 1.1%, respectively). It should be noted that medical histories of coronary artery disease (High level group term [HLGT] level) were more frequently reported at baseline in the S 12911 group than in the placebo group (20.7% *versus* 16.1%, respectively).
- *Skin and subcutaneous tissue disorders*: 14.5% *versus* 11.5%, respectively, mainly pruritus (5.2% *versus* 4.6%, respectively).
- *Metabolism and nutrition disorders*: 11.0% *versus* 8.0%, respectively, mainly hypercholesterolaemia (2.9% *versus* 1.1%, respectively).

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SUMMARY - CONCLUSIONS (Cont'd)
SAFETY RESULTS (Cont'd)

In both groups, the most frequently reported emergent adverse events were hypertension (10.4% *versus* 11.5% in the placebo group) and back pain (8.7% and 12.6%, respectively). Arthralgia was reported in 5.8% *versus* 11.5% and nasopharyngitis in 5.2% *versus* 10.3%. Some EAEs were more frequently reported in the S 12911 group than in the placebo group, including headache (4.6% *versus* 1.1%, respectively) - expected with S 12911 treatment -, angina pectoris (4.0% *versus* none, respectively), gastroenteritis (3.5% *versus* none, respectively) and coronary artery disease (3.5% *versus* 1.1%, respectively).

10 non-vertebral fractures in 10 patients were reported during the study on treatment, with an incidence rate that was lower in the S 12911 group than in the placebo group: 3.5% (6 patients) *versus* 4.6% (4 patients), 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 (93.9% of the events). **Severe emergent adverse events** were less frequently reported in the S 12911 group than in the placebo group: 28 patients (16.2%) *versus* 22 patients (25.3%), respectively. No relevant between-group difference was detected as regards the nature and the frequency of these severe events.
Most of the EAEs (69.7% in the S 12911 group *versus* 75.1% in the placebo group) recovered or were recovering/improving.

Treatment-related emergent adverse events were reported with a similar frequency in each treatment group: 28.9% (50 patients) in the S 12911 group *versus* 29.9% (26 patients) in the placebo group. Most of these events were expected with S 12911 and listed in the current Summary of Product Characteristics. They were mainly due to *gastrointestinal disorders*: 8.7% *versus* 11.5%, respectively, and *skin and subcutaneous disorders*: 8.7% *versus* 3.4%, respectively. Most frequent preferred terms reported were: pruritus (2.9% *versus* 2.3%, respectively), diarrhoea (2.3% in each treatment group), dyspepsia and headache (2.3% *versus* none, each one, respectively).

Premature discontinuations of treatment due to adverse events were more frequent in the S 12911 group than in the placebo group: 17.9% (31 patients) *versus* 13.8% (12 patients), respectively. Events responsible for treatment withdrawal concerned mainly *gastrointestinal disorders* (4.6% *versus* 5.7%, 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). The difference between the total of patients who were prematurely discontinued treatment and that of the patients withdrawn for adverse event was due to 3 patients who died (sudden death and unknown cause in the S 12911 group and cerebral haemorrhage in the placebo group).

Emergent serious adverse events were reported with a similar frequency overall in each treatment group: 29.5% (51 patients) in the S 12911 group *versus* 29.9% (26 patients) in the placebo group. The most frequently affected system organ classes were *cardiac disorders* (in 6.4% of the patients in the S 12911 group *versus* 4.6% in the placebo group), and *infections and infestations* (4.0% and 3.4%, respectively). In the S 12911 group, the preferred term reported more than once were: prostate cancer (4 patients), inguinal hernia (3 patients), coronary artery disease (3 patients), and reported in 2 patients were: acute myocardial infarction, angina pectoris, pneumonia, osteoarthritis, spinal osteoarthritis, femur fracture, deep vein thrombosis, and iron deficiency anaemia. Both cases of deep vein thrombosis were considered treatment-related, led to treatment withdrawal and were improving/recovering at the end of the study.

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

During the treatment period, there were 3 deaths (1.7%) in the S 12911 group (septic shock, death of unknown cause, and sudden death) and 1 death (1.1%) in the placebo group from cerebral haemorrhage; none were considered as treatment-related according to the investigator. The patients who died from sudden death and unknown cause, both had histories of cardiovascular diseases.

In addition, one further death occurred more than one year after the last study drug intake: a road traffic accident in a patient randomised to S 12911.

Laboratory tests

Neither clinically relevant changes nor differences between groups over time were detected for **biochemical** parameters, except for CPK. The mean CPK level increased from baseline to last value in the S 12911 group (mean change = 21.0 ± 74.1 IU/L) whereas it remained stable in placebo group (-3.4 ± 46.7 IU/L). No potentially clinically significant abnormal (PCSA) values were reported.

PCSA values were sparse for biochemical parameters, except for phosphorus for which high emergent PCSA values were detected in 17 patients (10.8% of the assessable patients) in the S 12911 group *versus* 2 patients (2.5%) in the placebo group. The effects of S 12911 on phosphocalcic parameters were expected according to the mechanism of action of strontium ranelate and were observed in previous studies.

No clinically relevant change over time or between-group difference was detected for **haematological** parameters, except for platelet counts for which low out-of-reference range values were more frequently reported in the S 12911 group than in the placebo group (13.4% *versus* 7.5%, respectively), and low out-of-reference range values for haemoglobin (12.1% *versus* 8.6%, respectively). Emergent (low or high) PCSA values for haematological parameters affected 10 patients (5.8%) in the S 12911 group *versus* 2 (2.3%) in the placebo group, mainly for WBC (5 patients in S 12911 group) and haemoglobin (2 patients in S 12911 group).

No clinically relevant change over time or between-group difference was detected for **haemostasis** parameters except for factor VIII, for which a mean increase over time was observed in both treatment groups: 21.3 ± 52.8% in the S 12911 group and 21.2 ± 44.1% in the placebo group. High PCSA values were detected for factor VIII in 7.9% of patients in the S 12911 group and 10.0% in the placebo group. None of these patients were affected by deep vein thrombosis.

Vital signs and ECG

Neither clinically relevant changes over time nor differences between groups were detected for vital signs or ECG.

Vertebral fractures assessed by X-ray

The frequency of patients affected by a new osteoporotic vertebral fracture was lower in the S 12911 group than in the placebo group (7 patients, 5.8% of the 120 assessable patients *versus* 5 patients, 7.8% of the 64 assessable patients, respectively). Although no reliable conclusion can be drawn considering the low number of fractures, after 2 years, vertebral fracture in incidence was lower in the strontium ranelate group than in the placebo group.

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CONCLUSIONS

This study was designed as a bridging study to confirm the positive effects of S 12911 on BMD augmentation in men, since this has been demonstrated in pivotal Phase III studies in women. The baseline characteristics of the patients were in keeping with the target population defined in the protocol. Compliance and exposure to treatment were satisfactory. Serum strontium levels in treated patients reached the same levels as in previous Phase III studies.

Lumbar L2-L4 BMD (main efficacy criterion) increased by about 10% after 2 years of treatment with S 12911 *versus* an increase of about 2% in the placebo group – resulting in an estimate of the between-group difference of 7.7% ($p < 0.001$). Thus, the significant result demonstrated after 1 year of treatment (estimated difference = 5.3%, $p < 0.001$) was consolidated over 2 years and is consistent with results in the much larger SOTI/TROPOS Phase III studies conducted in osteoporotic women.

Over the 2 years of treatment, the overall incidence of emergent adverse events was lower in the S 12911 group as compared to placebo, with a similar incidence of emergent serious adverse events. While there was a tendency towards an imbalance in the incidence of coronary artery disorder EAEs in the S 12911 group, this should be interpreted in the light of a similar imbalance in the relevant medical histories in the study population. In conclusion, the observed S 12911 safety profile was therefore in accordance with current knowledge.

The present study was not powered to assess the antifractural efficacy of S 12911 and the observed rate of new osteoporotic vertebral fractures was low. New vertebral fractures tended however to be less frequent in the active treatment group than on placebo (5.8% *versus* 7.8%). It is expected, following the demonstrated relationship between the increase in BMD and antifractural efficacy in previous Phase III studies in women (SOTI/TROPOS), that S 12911 will show similar antifractural efficacy in osteoporotic men.

Date of the report: 15 March 2012