Document title	**Clinical Study Report Synopsis**
Study title	**A double-blind, multicentric, multinational randomised study to assess the effects of (one year extended to) two years (Amendment No. 4) administration of 2g per day of strontium ranelate versus alendronate 70 mg per week in women with postmenopausal osteoporosis on bone microarchitecture measured by high resolution peripheral Quantitative Computed Tomography (p-QCT).**
Study drug	**Strontium ranelate (S 12911)**
Studied indication	**Postmenopausal osteoporosis**
Development phase	**Phase III**
Protocol code	**CL3-12911-019**
Study initiation date	**23 January 2006**
Study completion date	**26 February 2009**
Main coordinator	[redacted] **Switzerland**
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 Rue Carnot** **92284 Suresnes Cedex - France**
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 6 August 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:
A double-blind, multicentric, multinational randomised study to assess the effects of (one year extended to) two years (Amendment No. 4) administration of 2 g per day of strontium ranelate *versus* alendronate 70 mg per week in women with postmenopausal osteoporosis on bone microarchitecture measured by high resolution peripheral-Quantitative Computed Tomography (p-QCT).
Protocol No.: CL3-12911-019

Coordinator:
International Coordinator: [redacted]
National Coordinator for France: [redacted]

Study centres:
- Total number of centres: 8
- Total number of countries: 4

Number of centres/country: 3 in France, 2 in Switzerland, 1 in Australia, 2 in Germany.

Publication (reference): Not applicable

Studied period: Initiation date: 23 January 2006 Completion date: 26 February 2009	**Phase of development of the study: III**

Objective:
To assess the effects of strontium ranelate (2 g/day) (with calcium 500 mg/day and vitamin D 400 IU/day supplements) in comparison with alendronate (70 mg/week) (with calcium 500 mg/day and vitamin D 400 IU/day supplements) on the bone microarchitecture in patients with postmenopausal osteoporosis

Methodology:
Double blind, double dummy, randomised controlled study in postmenopausal osteoporotic women.

Number of patients:
Planned: 72 patients (36 per group).
Included: 88 included patients (46 patients in the strontium ranelate (SR) group and 42 patients in the alendronate group).

Diagnosis and main criteria for inclusion:
Post-menopausal women of at least 50 years with osteoporosis (total proximal femur or femoral neck T-score measured by DXA ≤ -2.5 (Nhanes III) or lumbar spine T-score ≤ -2.5 (according to the references of the manufacturer) corresponding to a mean femoral neck BMD of 0.558 g/cm² (if Hologic device) or 0.691 g/cm² if Lunar device).

Study treatment:
One S12911 2 g sachet once a day at bedtime associated with elemental calcium 500 mg/day and vitamin D 400 IU/day taken at lunchtime.
Batches No.'s: L0007846, L0014075, L0016500, L0018602.

Comparator: one capsule of alendronate 70 mg once a week at rising on an empty stomach associated with elemental calcium 500 mg/day and vitamin D 400 IU/day taken at lunchtime.

Duration of treatment: one year extended to 2 years by Amendment No. 4

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Criteria for evaluation:

Pharmacodynamy measurements:

Bone microarchitecture parameters measured at distal radius and distal tibia by p-QCT:

- Number of trabeculae
- Trabecular thickness
- Trabecular separation
- Cortical thickness
- Bone perimeter
- Structure Model Index
- Trabecular Bone volume to tissue volume
- Trabecular bone density
- Compact bone density
- Inhomogeneity of network

Lumbar and hip BMD by DXA

Bone markers (b-ALP, S-CTX)

Safety measurements: Biology, adverse events and vital signs

Statistical methods:

Study outcome: descriptive statistics were provided.

Efficacy:

The Full Analysis set (FAS, main analysis set) included all randomised patients who took at least one dose of the study treatment and with at least one baseline and one post-baseline assessable p-QCT evaluation.

The type I error rate was set at the 5% threshold (two-sided test).

Primary efficacy criteria: non-corrected calibrated bone microarchitecture parameters on tibia and radius

Primary analyses: The non-corrected calibrated bone microarchitecture parameters were mainly expressed as relative changes from baseline to the last post-baseline value on treatment until M24 (End). The comparison between SR group and alendronate group was performed using a linear model with centre as covariate (fixed effect). Estimate of the difference between adjusted group means, its standard error, 95% confidence interval (CI) and corresponding p-value were provided.

The robustness was checked using a similar model using centre as a random effect covariate, and using a non-parametric approach without adjustment, based on the Hodges-Lehmann's estimator with p value issued from the Mann-Withney Wilcoxon test.

The change from baseline to End was also analysed using a linear model studying treatment effect with baseline and centre (fixed effect) as covariates.

Secondary analyses included the within-group evolution analysis, tested in each treatment group using a two sided Student's t test for paired sample (parametric approach) and a Wilcoxon signed-rank test (non parametric approach).

Secondary efficacy criteria:

Lumbar L1-L4, femoral neck and total hip BMD: groups were compared on the relative change from baseline to each visit and End using a linear model studying treatment effect with centre as covariate (fixed effect), and on the change from baseline to each visit and End using a linear model studying treatment effect with baseline and centre (fixed effect) as covariates. The within group evolution was tested using a two-sided Student's t test for paired sample.

Bone markers: groups were compared on the relative change and the change from baseline to each visit and End using a linear model studying treatment effect with centre as covariate (fixed effect). The robustness was checked using a non-parametric approach without adjustment, based on the Hodges-Lehmann's estimator (for relative change) .

Safety: descriptive statistics were provided in the Safety Set.

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SUMMARY-CONCLUSIONS

STUDY POPULATION AND OUTCOME

Overall disposition of patients is summarised below.

Overall patients disposition

	SR	**Alendronate**	**All**
Included (randomised)	**46**	**42**	**88**
In compliance with the protocol	24	28	52
With a protocol deviation at inclusion	22	14	36
Withdrawn due to	**16**	**14**	**30**
Adverse event	7	4	11
Protocol deviation	2	1	3
Non-medical reason	7	9	16
Lost to follow-up	**-**	**1**	**1**
Completed	**30**	**27**	**57**
In compliance with the protocol	18	19	37
With a protocol deviation during the study	12	8	20

A total of 88 patients were included: 46 patients in the SR group and 42 patients in the alendronate group. 84 patients were still in the study (45 patients in the SR group and 39 patients in the alendronate group) at M12 and 57 patients completed the study (30 patients in the SR group and 27 patients in the alendronate group). One patient was lost to follow-up.

Premature discontinuation of the study treatment concerned 30 patients (34.1%): 16 patients (34.8%) in the SR group and 14 patients (33.3%) in the alendronate group. The reasons for stopping were:

- Adverse event for 11 patients: 7 in the SR group and 4 in the alendronate group.
- Non-medical reason for 16 patients: 7 patients in the SR group and 9 in the alendronate group.
- Protocol deviation for 3 patients, 2 in the SR group (non-compliance and unauthorised treatment) and one patient in the alendronate group who stopped the supplementation of calcium vitamin D.

At inclusion, 36 patients (40.9%) presented 42 protocol deviations, mainly concerning patients included without all biology results (22.7%). During the study, 51 patients (58.0%) reported 88 protocol deviations, the most frequent being overall exposure to treatment < 18 months (27.3%) and incomplete biology results (20.5%). Deviations at inclusion and during the study were well balanced in the two groups.

Main baseline characteristics are summarised below.

Baseline characteristics in the Randomised Set (N = 88)

Parameters (unit)		**SR (N = 46)**	**Alendronate (N = 42)**	**All (N = 88)**
Age (years)	Mean ± SD	63.8 ± 7.3	63.7 ± 7.5	63.8 ± 7.3
BMI (kg/m²)	Mean ± SD	22.98 ± 3.34	22.65 ± 2.75	22.83 ± 3.06
Time since menopause (years)	Mean ± SD	15.2 ± 7.6	16.5 ± 8.8	15.9 ± 8.2
Time since diagnosis of osteoporosis (months)	Mean ± SD	22.4 ± 38.4	11.8 ± 32.3	17.4 ± 35.8
	Median	2.0	2.0	2.0
Lumbar L1-L4 BMD (g/cm^2)	Mean ± SD	0.745 ± 0.086	0.733 ± 0.092	0.740 ± 0.088
T-score	Mean ± SD	-2.741 ± 0.778	-2.853 ± 0.836	-2.794 ± 0.803
Femoral neck BMD (g/cm^2)	Mean ± SD	0.617 ± 0.094	0.608 ± 0.093	0.613 ± 0.093
T-score	Mean ± SD	-2.009 ± 0.787	-2.081 ± 0.775	-2.043 ± 0.778
Total hip BMD (g/cm^2)	Mean ± SD	0.691 ± 0.081	0.689 ± 0.094	0.690 ± 0.087
T-score	Mean ± SD	-2.059 ± 0.664	-2.076 ± 0.772	-2.067 ± 0.713

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STUDY POPULATION AND OUTCOME (Cont'd)

Patient's characteristics were in agreement with the objectives of the study and were similar in the two treatment groups. Age of the randomised patients ranged from 51 to 79 years with a mean ± SD of 63.8 ± 7.3 years. BMI ranged from 16.7 to 32.9 kg/m² with a mean of 22.8 ± 3.1 kg/m². The time since menopause ranged from 5 to 39 years with a mean of 15.9 ± 8.2 years. All patients presented primary osteoporosis and mean time since diagnosis was 17.4 ± 35.8 months. All patients were ambulatory.

Baseline BMD parameters and bone microarchitecture criteria were very close in the two treatment groups.

Most patients reported medical history other than osteoporosis, mainly back pain (29.5%), hypercholesterolaemia (21.6%) and hypertension (20.5%). The main concomitant treatments at selection were proton pump inhibitors (14.8%), anilides (14.8%), calcium in combination with other drugs (13.6%) and benzodiazepines (12.5%). Calcium supplements and vitamin D were prescribed to all patients at inclusion.

The mean duration of treatment until M24 was 19.5 ± 6.8 months and was similar for capsules and sachets. Most patients (63.6%) had a treatment duration between 23 and 25 months. Global compliance was satisfactory: 89.6 ± 16.8% (sachets) and 93.4 ± 12.8% (capsules).

Strontium serum level in the SR group had reached the steady state at M3. At M12, mean strontium serum level was 125.1 ± 74.3 µmol/L, which was consistent with levels obtained in previous studies.

EFFICACY RESULTS

Primary assessment criterion: bone microarchitecture parameters

The FAS consisted of 83 patients of whom 80 (41 in the SR group and 39 in the alendronate group) had assessable tibia examinations.

For the tibia, cortical thickness increased by 6.29 ± 9.53 % in the SR group and was unchanged (0.93 ± 6.23%) in the alendronate group. Trabecular bone volume (to tissue volume) increased by 2.48 ± 5.13% in the SR group *versus* 0.84 ± 3.81% in the alendronate group. Trabecular bone density increased by 2.47 ± 5.0 % in the SR group *versus* 0.88 ± 4.00% in the alendronate group. Compact bone density increased by 1.43 ± 2.77% in the SR group *versus* 0.36 ± 2.1 % in the alendronate group.

For these four parameters, the between-group differences in the relative changes in favour of SR were statistically significant. Furthermore, the between-group differences in the mean changes were also statistically significant, and the within-group evolution over time was statistically significant only in the SR group. The change over time was statistically significant in the SR group for cortical thickness from 3 months ($p < 0001$) and for trabecular bone volume to tissue volume from 6 months ($p = 0.0336$).

There was no statistically significant between-group difference for other parameters.

Changes observed on distal radius were of lower magnitude than those observed on tibia. In addition, the number of assessable examinations was only 36 in the SR group and 28 in the alendronate group. A statistically significant effect of SR *versus* alendronate on the relative change was found for compact bone density: relative change was 1.08 ± 2.46 % in the SR group *versus* -0.27 ± 1.93 % in the alendronate group. No other relevant between-group differences were detected.

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EFFICACY RESULTS (Cont'd)

Relative changes (%) from baseline to end in non-calibrated bone microarchitecture parameters (tibia) in the FAS

Parameter	**Relative changes from baseline to End (%)**		**Between-group difference** (parametric approach)		
	SR (N = 42)	**Alendronate (N = 41)**	**E (SE)[1]**	**95%CI[2]**	**p value[3]**
Number of assessable p-QCT exams*	41	39			
	Mean ± SD	**Mean ± SD**			
Number of trabeculae (N/mm)	3.55 ± 9.28	4.56 ± 9.96	-1.070 (2.079)	[-5.212 ; 3.072]	0.6083
Trabecular thickness (mm)	-0.54 ± 8.70	-2.95 ± 8.11	2.610 (1.908)	[-1.192 ; 6.411]	0.1755
Trabecular separation (mm)	-2.96 ± 8.68	-3.60 ± 9.70	0.720 (1.986)	[-3.238 ; 4.678]	0.7180
Cortical thickness (mm)	6.29 ± 9.53	0.93 ± 6.23	5.411 (1.836)	[1.752 ; 9.069]	**0.0043**
Bone perimeter (mm)	-0.10 ± 0.39	-0.09 ± 0.29	0.002 (0.074)	[-0.146 ; 0.149]	0.9817
Structure Model Index (S.M.I.)	2.57 ± 9.12	4.61 ± 10.23	-1.921(2.110)	[-6.125 ; 2.283]	0.3655
Trabecular bone volume (to tissue volume)	2.48 ± 5.13	0.84 ± 3.81	1.783 (0.852)	[0.085 ; 3.481]	**0.0399**
Trabecular bone density (mg/cm^3)	2.47 ± 5.07	0.88 ± 4.00-	1.729 (0.859)	[0.019 ; 3.440]	**0.0476**
Compact bone density (mg/cm^3)	1.43 ± 2.77	0.36 ± 2.14	1.137 (0.530)	[0.080 ; 2.194]	**0.0353**
Inhomogeneity of network (mm)	-1.78 ± 10.14	-2.09 ± 13.01	0.490 (2.615)	[-4.720 ; 5.701]	0.8518

** with good or very good quality; (1) Estimate of the (centre as fixed effect) adjusted means difference SR–alendronate (Standard Error) (2) 95% Confidence Interval of the estimate; (3) Corresponding p value*

Mean changes from baseline to end in non-calibrated bone microarchitecture parameters (tibia) in the FAS

Parameter	**Changes from baseline to End**			
	SR (N = 42)		**Alendronate (N = 41)**	
Number of assessable p-QCT exams*	41		39	
	Mean ± SD	**p [1]**	**Mean ± SD**	p [1]
Number of trabeculae (N/mm)	0.042 ± 0.128	**0.043**	0.056 ± 0.133	**0.013**
Trabecular thickness (mm)	-0.001 ± 0.007	0.437	-0.003 ± 0.006	**0.015**
Trabecular separation (mm)	-0.021 ± 0.058	**0.024**	-0.026 ± 0.061	**0.011**
Cortical thickness (mm)	0.036 ± 0.042	**< 0.0001**	0.007 ± 0.039	0.266
Bone perimeter (mm)	-0.10 ± 0.41	0.107	-0.09 ± 0.32	0.075
Structure Model Index (S.M.I.)	0.03 ± 0.16	0.212	0.07 ± 0.15	**0.010**
Trabecular bone volume (to tissue volume)	0.002 ± 0.004	**0.0001**	0.001 ± 0.003	0.243
Trabecular bone density (mg/cm^3)	2.9 ± 4.4	**0.0002**	0.8 ± 4.1	0.248
Compact bone density (mg/cm^3)	10.0 ± 18.7	**0.001**	2.5 ± 15.8	0.324
Inhomogeneity of network (mm)	-0.004 ± 0.060	0.655	-0.011 ± 0.062	0.282

** with good or very good quality; (1) Within group difference, two-sided Student's t test for paired samples / p-value is to compare with alpha=5%*

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EFFICACY RESULTS (Cont'd)

Secondary criteria

Lumbar, total hip and femoral neck BMD increased significantly in both groups from baseline to last value with no relevant differences between groups:

- Mean lumbar L1-L4 BMD increased by 6.46 ± 6.25% in the SR group and by 5.55 ± 4.26% in the alendronate group.
- Mean femoral neck BMD increased by 4.72 ± 4.30% in the SR group and by 3.27 ± 4.02%, in the alendronate group.
- Mean total hip BMD increased by 3.95 ± 4.55% in the SR group and by 2.98 ± 2.40%, in the alendronate group.

Analyses on **bone markers** gave the following expected results:

- Mean change from baseline to last value in b-ALP was 2.30 ± 3.62 ng/mL in the SR group and -4.14 ± 3.09 ng/mL in the alendronate group.
- Mean change from baseline to last value in S-CTX was -0.1189 ± 0.2440 ng/mL in the SR group and -0.4226 ± 0.2255 ng/mL in the alendronate group.

This simultaneous increase in b-ALP, a marker of bone formation and decrease in S-CTX, a marker of bone resorption, observed in the SR group is consistent with the dual mechanism of action of SR.

SAFETY RESULTS

Main safety results are summarised in the table below.

Main safety results

		SR (N = 46)	**Alendronate (N = 42)**
Patients having reported			
At least one emergent adverse event	n (%)	42 (91.3)	39 (92.9)
At least one treatment-related emergent adverse event	n (%)	16 (34.8)	14 (33.3)
At least one treatment related gastrointestinal disorders	n (%)	7 (15.2)	10 (23.8)
Patients having experienced			
At least one non-fatal serious adverse event	n (%)	5 (10.9)	6 (14.3)
At least one treatment-related serious adverse event	n (%)	-	-
Patients withdrawn			
Due to an adverse event	n (%)	7 (15.2)	4 (9.5)
Due to a serious adverse event	n (%)	-	1 (2.4)
Due a treatment-related adverse event	n (%)	6 (13.0)	3 (7.1)
Due a treatment-related serious adverse event	n (%)	-	-
Patients who died	n (%)	-	1 (2.4)

Emergent adverse events

The frequency of patients who reported at least one **emergent adverse event** was similar in both treatment groups: 42 patients in the SR group (91.3%) and 39 patients in the alendronate group (92.9%). The most frequently affected system organ classes were infections and infestations (41.3% of the patients in the SR group *versus* 40.5 % in the alendronate group), musculoskeletal, connective and bone disorders (41.3% *versus* 38.1%, respectively) and gastrointestinal disorders (34.8% *versus* 31.0% respectively).

The most common emergent adverse events were bronchitis (15.2% in the SR group *versus* 11.9% in the alendronate group), hypertension (10.9% *versus* 9.5%, respectively), back pain (8.7% *versus* 11.9%) and localised osteoarthritis (8.7% *versus* 7.1%).

One lumbar vertebral fracture was reported in the SR group *versus* none in the alendronate group.

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SAFETY RESULTS (Cont'd)

There was no relevant difference between treatment groups regarding the system organ classes affected and the nature and frequency of emergent adverse events.

Most emergent adverse events were of mild or moderate intensity.

Severe emergent adverse events occurred in 17 patients, 10 patients (21.7%) in the SR group and 7 patients (16.7%) in the alendronate group. None of these events were reported more than once; 3 of them were considered treatment-related: dysphagia and night cramps in the SR group and flatulence in the alendronate group.

Treatment-related emergent adverse events were reported with the same frequency in the two treatment groups: 16 patients (34.8%) in the SR group and 14 patients (33.3%) in the alendronate group. The most frequent were related to gastrointestinal disorders: 7 patients (15.2%) in the SR group and 10 patients (23.8%) in the alendronate group.

Overall, 11 patients **discontinued the treatment due to adverse events,** 7 patients (15.2%) in the SR group (following: pruritis, rash, superficial phlebitis, sleep disorders, nausea, keratocunjunctivitis sicca and chronic obstructive airways disease) and 4 patients (9.5%) (peptic ulcer, abdominal pain upper, nausea and breast cancer) in the alendronate group. One of the events (breast cancer) reported in the alendronate group was serious and considered not related to the study drug.

Deaths and non-fatal serious adverse events

One patient in the alendronate group died from cerebral haemorrhage which occurred 124 days after the last study drug intake.

Overall, 11 patients (12.5%) experienced at least one non-fatal emergent serious adverse event (SAE):

- 5 patients (10.9%) in the SR group experienced 7 SAE: Benign colonic polyp, cataract, colon adenoma, varicose vein/Morton's Neuroma in the same patient and intestinal obstruction/incisional hernia in the same patient.
- 6 patients (14.3%) in the alendronate group experienced 9 SAE: goitre, radial nerve injury, breast cancer, lipoma, pneumonia and in the same patient: human papilloma virus serology positive/toe deformity (right then left foot).

None of the serious adverse events were considered related to the study drug by the investigator. In the SR group, all of them resolved and none led to study drug withdrawal.

Laboratory tests

The mean CPK levels slightly decreased in both groups. The number of patients with at least one emergent high out-of-reference range CPK value was higher in the SR group than in the alendronate group: 8 patients and 4 patients, respectively. The abnormal values were above the upper limit of the alert range in two patients (3.3 and 3.7 ULN for re-test and 3.8 ULN). In both cases, the adverse event reported recovered and was considered unrelated to the study drug, and the CPK value decreased at the following visit despite the study drug continuation.

Mean creatinine was stable over time in both treatment groups. Abnormal values were sparse with no between-group difference. No potentially clinically significant values were reported.

Mean blood calcium slightly decreased in the SR group. Low out-of–reference-range calcium values (*i.e.* < 2.23 mmol/L) were reported in 19 patients in the SR group and 3 patients in the alendronate group. None of these values were considered clinically significant by the investigator and none was outside the alert range.

Vital signs

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

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CONCLUSION

In summary, 88 patients were included in this 2-year study, aimed at assessing the effects of strontium ranelate in comparison with alendronate on the bone microarchitecture in patients with postmenopausal osteoporosis. Strontium ranelate was associated with a significant improvement *versus* alendronate on the microarchitecture parameters with increase in cortical thickness, trabecular bone volume to tissue volume, trabecular bone density and compact bone density of the distal tibia. The observed improvement in bone structure and density with strontium ranelate together with results on bone markers are consistent with previous findings showing an increase in bone formation and a decrease in bone resorption with strontium ranelate.

Strontium ranelate was well tolerated. Safety results were in accordance with those obtained in previous phase III studies and with the summary of product characteristics of strontium ranelate, with no unexpected adverse event.

Date of the report: 6 August 2010