Document title	**Clinical Study Report Synopsis**
Study title	**A double-blind, multicenter, international randomised study to assess the effects of 6 months or 12 months administration of 2g per day of strontium ranelate *versus* alendronate 70mg per week by histomorphometry in women with postmenopausal osteoporosis.**
Study drug	**S 12911**
Studied indication	**Treatment of post-menopausal osteoporosis**
Development phase	**Phase III**
Protocol code	**CL3-12911-025**
Study initiation date	**07 June 2007**
Study completion date	**11 February 2010**
Main coordinator	[redacted] **France**
Company / Sponsor	**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 H7H 4A7 - Canada** **Servier Research and Development** **Wexham Springs, Framewood Road** **Wexham, Slough SL3 6RJ - UK**
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 26 March 2012**

~~**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: A double-blind, multicenter, international randomised study to assess the effects of 6 months or 12 months administration of 2 g per day of strontium ranelate *versus* alendronate 70 mg per week on bone remodelling and bone safety assessed by histomorphometry in women with postmenopausal osteoporosis.
Protocol No.: CL3-12911-025

International Coordinator:
[redacted]

Study centres:
Multicentric study (34 active centres, 11 countries, 388 included patients)
Argentina (5 centres, 70 patients), Australia (3 centres, 9 patients), Brazil (4 centres, 76 patients), Canada (1 centre, 21 patients), Czech Republic (5 centres, 69 patients), Denmark (2 centres, 20 patients), Estonia (1 centre, 40 patients), Hungary (5 centres, 34 patients), Italy (1 centre, 3 patients), Mexico (5 centres, 32 patients), Poland (2 centres, 14 patients).

Publication (reference): NA

Studied period: Initiation date: 07 June 2007 Completion date: 11 February 2010	**Phase of development of the study:** III

Objectives:
The **main** objective of this study was to assess the effects of 6 or 12 months treatment with strontium ranelate (2 g/day) in comparison with alendronate (70 mg/week) on bone formation assessed by histomorphometry on transiliac paired biopsies performed in patients with postmenopausal osteoporosis treated for one year.
The **secondary** objectives of this study were to assess:
- The effects of 6 or 12 months treatment with strontium ranelate (2 g/day) compared to baseline on bone histomorphometry parameters of formation, resorption and structure.
- The effects of strontium ranelate (2 g/day) on histomorphometry parameters including safety parameters, secondary mineralization, bone architecture assessed by microcomputerised tomography (microCT), bone markers, bone mineral density (BMD), in comparison with alendronate (70 mg/week).

To note, biopsies were performed in both treatment groups at M6 and 12, but results from the alendronate M6 and M12 groups were pooled (for details please refer to statistical method).

Methodology:
Double blind, double dummy, randomised controlled study in postmenopausal osteoporotic women, with a randomisation ratio 2:1 (S 12911: alendronate).

Number of patients:
Planned: 285 patients (190 patients in the S 12911 group and 95 patients in the alendronate group).
Randomised: 387 patients (256 patients in the S 12911 group and 131 patients in the alendronate group).

Diagnosis and main criteria for inclusion:
- Ambulatory women, ≥ 50 years old (with no upper age limit, restricted to between 50 and 90 years by amendment No. 3 in Argentina), written informed consent
- Postmenopausal for at least 3 years and osteoporotic defined as:
  - T-score at the spine and /or hip ≤ -2.5 SD or T-score at the spine and /or hip ≤ -1 SD and at least one prevalent low trauma fracture modified according to Amendment No. 4 by:
  - T-score at the lumbar L1/L4 and/or femoral neck level ≤ -2.5 SD or T-score at the lumbar L1-L4 and/or femoral Neck level ≤ -1 SD and at least one prevalent low trauma fracture

Study drug:
One S 12911 2 g sachet once a day at bedtime associated with elemental calcium 1000 mg/day and vitamin D 800 IU/day (CalperosD3®, 2 tablets/day) in two daily doses taken at breakfast and at dinner. In addition, in order to maintain the blind, one capsule of placebo of alendronate was received by the patients once a week.

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Comparator: One capsule of alendronate 70 mg once a week at rising on an empty stomach associated with elemental calcium 1000 mg/day and vitamin D 800 IU/day (CalperosD3®) in two daily doses taken at breakfast and at dinner. In addition, in order to maintain the blind, one sachet of placebo of S 12911 was received by the patients daily at bedtime.

Duration of treatment:

- 6-7 weeks run-in (supplementation with calcium 1000 mg/day and vitamin D 800 IU/day).
- One year S 12911 2 g/day or alendronate 70 mg once a week, in addition with calcium 1000 mg/day and vitamin D 800 IU/day.

Criteria for evaluation:

Efficacy:

Transiliac biopsy was performed after double labeling with tetracycline at baseline and either after 6 months of treatment for 50% of patients or after 1 year of treatment for 50% of patients, determined by randomisation, but all patients were treated and followed for 1 year. The post-baseline biopsy was to be performed on the opposite side of the baseline one. Histomorphometry parameters were centrally assessed.

Primary assessment criterion:

Cancellous Mineralizing Surfaces to bone surface (Cn.MS/BS, %): Bone formation parameter measured by histomorphometry on paired transiliac biopsies.

Secondary criteria:

- Other bone histomorphometric parameters assessed in Cortical (Ct), Cancellous (Cn), Endocortical (Ec), and Cn+En *i.e.* Es, bone at baseline and after 6 or 12 months of treatment:
  - Formation parameters:
    - *Dynamic parameters:* **Mineralizing Surface to Bone Surface** (MS/BS %) (Ec, Es), **Bone Formation Rate (BFR)/BS** ($\mu m^3/\mu m^2$/day) (Cn, Ec and Es), Cn Activation Frequency Ac f (/year), Cn Osteoid Maturation Time (day).
    - *Static parameters:* Osteoblast Surface (Ob.S)/BS (%) (Cn, Ec and Es), Osteoid Surface (OS)/BS (%) (Cn, Ec and Es), Cn Osteoid Volume / Bone Volume (%) (OV/BV), Osteoid Thickness (µm) (Cn, Ec and Es).
  - Mineralization parameters: **Mineral Apposition Rate** (MAR, µm/d) (Ct, Cn and Es), Cn mineralization Lag Time (day).
  - Resorption parameters: Eroded Surface (ES/BS, %) (Cn, Ec and Es), Cn Eroded Volume/Bone Volume, Osteoclast Surface (Oc.S/BS, %) (Cn, Ec and Es), Osteoclast number NOc/BS (mm) (Cn, Ec and Es), Cn mean erosion depth (µm), Cn max erosion depth (µm).
  - Structure parameters: **Trabecular Thickness** (Tb.Th, µm), **Trabecular Number** (TbN, mm), **Trabecular Separation** (Tb.Sp, µm), **Cortical Thickness** (Ct.Th, µm), **Cortical Porosity** (Ct.Po, %), Wall Thickness (W.Th, µm), **Bone Volume/Tissue Volume** (BV/TV, %), Cn node number/ tissue volume (mm^2).

    Note: efficacy parameters presented above were evaluated in two steps by the central reading centre: parameters in bold were assessed before breaking the blind. The other parameters were assessed and analysed after breaking the blind. However, the central reading centre was blinded to treatment.
- MicroCT and microradiography parameters at baseline and after 6 or 12 months of treatment:
  - MicroCT parameters: Cancellous bone volume per tissue volume (BV/TV, %), number of Trabeculae (Tb.N, /mm), Trabecular Thickness (Tb.Th, µm), Trabecular Separation (Tb.Sp, µm), Cortical Thickness (Ct.Th, µm), Cortical Porosity (Ct.Po, %), structure Model Index (SMI), Degree of Anistropy (DA), Connectivity Density (CD, mm^3).
  - Microradiography: Mean degree of mineralization of the bone (MDMB, g/cm^3), heterogeneity index (g/cm^3).
- Lumbar, femoral neck and hip BMD by DXA at baseline, M6 and M12.

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Criteria for evaluation (Cont'd)

- Bone markers: bone-alkaline phosphatase (b-ALP), C-Telopeptide Cross-links of type I collagen (s-CTX), N-terminal propeptide of type I procollagen (PINP), Osteoprotegerin (OPG) at selection, M3, M6 and M12 visits. Receptor Activator Nuclear factor Kappa B ligand and Inteleukin 6 initially planned was finally not assayed.

Safety

- Adverse events.
- Laboratory safety parameters: biochemistry (25(OH) vitamin D, phosphorus, calcium, creatinine, albumin, alkaline phosphatase, creatine phosphokinase and isoenzyms, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, creatinine clearance, alpha 1-globulin, alpha 2-globulin, beta-globulin, gamma globulin), haematology (full blood cell count, haemoglobin, haematocrit, mean corpuscular colume), urinary analysis (calcium and creatinine), coagulation analysis (activated partial thromboplastin time and prothrombin time) and hormonal analysis (intact parathyroid hormone) assessed at ASS1, ASS2, M6 and M12.
- Vital signs: weight, height, body mass index, sitting blood pressures and heart rate at each visit.
- Serum Strontium levels at selection, M3, M6 and M12 visits.
- Bone sample quality: biopsy general quality, marrow anomalies, bone anomalies, osteomalacia.

Pharmacokinetics

- Bone Strontium Content (Sr/(Sr +calcium (Ca)) ratio) at baseline and after 6 or 12 months of treatment.

Statistical methods:

Efficacy analysis

Primary efficacy criterion: Cancellous Mineralizing Surfaces to Bone Surface (MS/BS):

Main analysis:

The main analysis was performed in the FAS, defined as all patients from the Randomised Set having taken at least one dose of the study treatment and having at least one baseline and one post-baseline evaluation of the primary criterion Cn.MS/BS. Patients from the S 12911 group were split into two groups according to the actual visit of the second biopsy: S 12911 M6 group and S 12911 M12 group. The data from the alendronate group biopsies at M6 and M12 were pooled as the maximum effect is observed as soon as 6 months of treatment with alendronate (Arlot, 2005). The change in MS/BS between baseline and M6 in the S 12911 M6 group and the change in MS/BS between baseline and M12 in the S 12911 M12 group were compared to the change between baseline and the last post-baseline value in the alendronate group using a general linear model (Dunett, multiple comparaison procedure) with treatment group as the factor of interest and country and baseline MS/BS value as covariates. Adjusted mean differences, 95% Confidence Interval (CI) and the associated p-value (adjusted according to the procedure of Dunnett-Hsu) were provided. The last post-baseline value (End) in each treatment group was M6 or M12. As data from M6 and M12 were pooled in the alendronate group, the last post-baseline values taken into account for the analysis were those from the M6 and M12 biopsies.

Sensitivity analyses:

- A non-parametric approach (covariance analysis with the same model as the one used for the main analysis but using another norm) was performed in the FAS.
- The same analyses as the main one were performed:
  - In the Per Protocol Set 1 (PPS1), defined as all patients from the FAS who fulfilled at least the main following conditions: having a strontium level greater or equal to 80 µmol/L (for patients of the S 12911 group) or an overall compliance ≥ 65% and an overall exposure to the study treatment ≥ 9 months (for patients of the alendronate group).
  - In the PPS2, defined as all patients from the FAS who fulfilled at least the main following conditions: having a strontium level greater or equal to 40 µmol/L for patients of the S 12911 group and the same definition as the PPS1 for patients of the alendronate group.
- An analysis was also conducted with an adjustment on covariates (baseline, country, BMD and Vitamin D level) using a general linear model using Dunnett's multiple comparison procedure to compare the change from baseline value to END in the FAS: between the S 12911 2 g and alendronate groups.

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Statistical methods (Cont'd)

Secondary analyses:

Analyses on the changes were also performed on the relative changes.

Intragroup comparison within the S 12911 groups: the baseline MS/BS value was compared to M6 and M12 values, using a two-sided Student t test for paired samples.

Secondary criteria

- Other bone histomorphometry parameters: similar analyses as for the main efficacy criterion were performed.
- Micro CT and microradiography parameters: descriptive statistics were performed on the change and on the relative change from baseline to each visit and END.
- For BMD, both groups were compared on the change from baseline to each visit and to last value (End) using a general linear model with country and baseline as covariates. Similar analyses were performed for the relative change (without baseline adjustment). An intragroup comparison within the S 12911 group was also performed. Corrected and calibrated BMD data were used for statistical analysis.
- For bone markers, similar analyses were performed as for the main analysis of the primary efficacy criterion.

Safety analysis

Adverse events, laboratory parameters were assessed through descriptive statistics.

Pharmacokinetics analysis

Descriptive statistics were performed.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Overall disposition of patients is summarised below.

Overall patients disposition during the study

Status	**S 12911 (N = 256)**	**Alendronate (N = 131)**	**All (N = 387)**
	n (%)	**n (%)**	**n (%)**
Randomised	**256 (100)**	**131 (100)**	**387 (100)**
in compliance with the protocol	213 (83.2)	113 (86.3)	326 (84.2)
with a protocol deviation at inclusion	43 (16.8)	18 (13.7)	61 (15.8)
Lost to follow-up	**1 (0.4)**	**-**	**1 (0.3)**
Withdrawn due to	**40 (15.6)**	**9 (6.9)**	**49 (12.7)**
adverse event	22 (8.6)	4 (3.1)	26 (6.7)
non-medical reason	17 (6.6)	4 (3.1)	21 (5.4)
protocol deviation	1 (0.4)	1 (0.8)	2 (0.5)
Completed	**215 (84.0)**	**122 (93.1)**	**337 (87.1)**
in compliance with the protocol	162 (63.3)	96 (73.3)	258 (66.7)
with a protocol deviation during the study	53 (20.7)	26 (19.8)	79 (20.4)

n number of patients;% calculated as percentage of randomised patients in each treatment group

A total of 387 patients were randomised in the study: 256 patients in the S 12911 group and 131 patients in the alendronate group. Overall, 49 patients (12.7%) withdrew the study, mainly due to adverse events (8.6% in the S 12911 group *versus* 3.1% in the alendronate group) and non-medical reasons (6.6% *versus* 3.1%, respectively), with a higher percentage in the S 12911 group than in the alendronate group. A total of 337 patients completed the study: 215 patients (84.0%) in the S 12911 group and 122 patients (93.1%) in the alendronate group. Overall, 61 patients (15.8%) presented at least one protocol deviation at inclusion, and 128 patients (33.1%) presented at least one protocol deviation during the study, mainly bone biopsy not performed after the inclusion visit (15.5%). Protocol deviations were evenly distributed among the two treatment groups and did not appear to have a significant impact on the efficacy and safety assessments.

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SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME

Main baseline characteristics are summarised below.

Age of randomised patients ranged from 50 to 84 years with a mean ± SD of 63.6 ± 7.2 years. BMI ranged from 17.2 to 38.4 kg/m² with a mean ± SD of 25.8 ± 4.0 kg/m². All patients were ambulatory. Current smoking habits were reported in 39 patients (15.2%) in the S 12911 group and 27 patients (20.6%) in the alendronate group and current alcohol habits were reported in 51 patients (19.9%) in the S 12911 group and 23 patients (17.6%) in the alendronate group.

Hypertension was the most frequently reported medical history (34.4%) followed by osteoarthritis (31.5%). Consistently with the medical history, the most frequent concomitant treatments at inclusion were anti-inflammatory and antirheumatic products (23.5%) and agents acting on the renin-angiotensin system (21.2%).

All patients presented primary osteoporosis. Mean time since diagnosis was 20.9 ± 35.0 months (median = 4 months). Among randomised patients, 90 patients (23.3%) reported at least one prevalent osteoporotic fracture. A total of 169 patients (43.7%) reported at least one previous treatment for osteoporosis, mainly mineral supplement (calcium) (17.8%), calcium combinations with other drugs (12.9%), and vitamin D and analogues (16.8%).

Main baseline characteristics in the Randomised Set

			S 12911 (N = 256)	**Alendronate (N = 131)**	**All (N = 387)**
Age (years)		Mean ± SD	63.5 ± 7.3	63.8 ± 6.9	63.6 ± 7.2
		Min ; Max	51 ; 84	50 ; 79	50 ; 84
BMI (kg/m²)		Mean ± SD	25.9 ± 4.0	25.6 ± 4.0	25.8 ± 4.0
		Min ; Max	17.2 ; 38.4	17.2 ; 36.5	17.2 ; 38.4
Cancellous MS/BS (%)		n	241	123	364
		Mean ± SD	6.14 ± 4.40	5.69 ± 3.65	5.99 ± 4.16
		Min ; Max	0.00 ; 31.04	0.00 ; 17.22	0.00 ; 31.04
Lumbar L1-L4	BMD (mg/cm²)	Mean ± SD	787.0 ± 86.7	772.7 ± 90.5	782.2 ± 88.1
		Min ; Max	523.9 ; 1075.5	544.2 ; 997.8	523.9 ; 1075.5
	T-score	Mean ± SD	-2.87 ± 0.74	-2.99 ± 0.77	-2.91 ± 0.75
		Min ; Max	-5.10 ; -0.43	-4.93 ; -1.09	-5.10 ; -0.43
Femoral neck	BMD (mg/cm²)	Mean ± SD	675.8 ± 76.7	679.48 ± 84.09	677.1 ± 79.2
		Min ; Max	451.2 ; 871.2	492.5 ; 884.3	451.2 ; 884.3
	T-score	Mean ± SD	-2.20 ± 0.63	-2.17 ± 0.70	-2.19 ± 0.65
		Min ; Max	-4.06 ; -0.59	-3.71 ; -0.48	-4.06 ; -0.48
Total hip	BMD (mg/cm²)	Mean ± SD	744.1 ± 88.1	738.3 ± 95.6	742.1 ± 90.6
		Min ; Max	444.8 ; 967.6	527.0 ; 1001.9	444.8 ; 1001.9
	T-score	Mean ± SD	-1.72 ± 0.72	-1.77 ± 0.78	-1.74 ± 0.74
		Min ; Max	-4.16 ; 0.09	-3.49 ; 0.37	-4.16 ; 0.37
At least one prevalent osteoporotic fracture		n (%)	52 (20.3)	38 (29.0)	90 (23.3)

n number of patients; % calculated as percentage of the Randomised Set in each treatment group

There were no between-group differences in bone histomorphometry parameters, or in bone markers at baseline. The mean cancellous mineralizing surfaces to bone surface was 5.99 ± 4.16% in the Randomised Set, 6.14 ± 4.40% in the S 12911 group and 5.69 ± 3.65% in the alendronate group.

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SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

In the FAS, the mean duration of exposure was for sachets: 358.5 ± 30.1 days in the S 12911 M6 group and 360.4 ± 12.4 days in the S 12911 M12 group, and for capsules: 360.0 ± 15.0 days in the alendronate group. The majority of patients had a treatment exposure between 11 and 13 months (for sachets: 92.2% of patients in the S 12911 M6 group and 98.9% in the S 12911 M12 group, and for capsules: 95.5% in the alendronate group). The mean global compliances were 93.6 ± 8.6% for sachets in the S 12911 groups and 98.7 ± 7.0% for capsules in the alendronate group and were satisfactory (between 80 and 120%) in 92.2% of the patients for sachets and in 96.3% of the patients for capsules. The steady state of strontium level was observed from M3. At M12, the mean strontium level was 101.42 ± 68.16 µmol/L in the S 12911 group.

Baseline and demographic characteristics in the FAS, PPS1, and PPS2 were consistent with those described above for the Randomised Set.

EFFICACY RESULTS

Primary assessment criterion: cancellous mineralizing surfaces to bone surface (MS/BS)

Change from baseline to last value (End) in the FAS (main analysis): between-group (S 12911 groups versus alendronate) comparison

The changes from baseline to last value were –2.6 ± 5.5% in the S 12911 M6 group, –1.7 ± 5.5% in the S 12911 M12 group and –5.2 ± 3.5% in the alendronate (M6/M12) group group. The difference between each group of S 12911 and alendronate (M6/M12) group was statistically significant from baseline to End:

- S 12911 M6 group *versus* alendronate group: E (SE) = 2.73 (0.48), 95%CI = [1.67 ; 3.79], p < 0.001.
- S 12911 M12 group *versus* alendronate group: E (SE) = 4.65 (0.49), 95%CI = [3.57 ; 5.73], p < 0.001.

To note, the decrease in MS/BS from baseline to End was observed in all patients but one in the alendronate group, while 67.6% of the patients in the S 12911 group had a decrease and 32.4% had an increase in MS/BS.

The results were confirmed by the sensitivity analyses (non-parametric approach and parametric approach adjusted on risk factors).

The decrease in the mean cancellous MS/BS from baseline to End was lower in the S 12911 M12 group than in the S 12911 M6 group, with a statistically between-group difference (E (SE) = -1.93 (0.48, 95%CI = [-2.88 ;-0.97], p < 0.001, complementary analysis).

Cancellous mineralizing surfaces to bone surface: change from baseline to End in the FAS – Between-group comparison (S 12911 groups *versus* alendronate)

		S 12911 M6 (N = 90)	**S 12911 M12 (N = 89)**	**Alendronate (M6/M12) (N = 89)**
Baseline	Mean ± SD	5.53 ± 4.54	6.63 ± 4.25	5.40 ± 3.59
	Min ; Max	0.00 ; 31.04	0.35 ; 19.48	0.00 ; 17.22
End	Mean ± SD	2.94 ± 3.73	4.91 ± 4.15	0.24 ± 0.46
	Min ; Max	0.00 ; 26.69	0.00 ; 21.12	0.00 ; 3.41
Changes from baseline to end	Mean ± SD	-2.59 ± 5.45	-1.72 ± 5.53	-5.16 ± 3.53
	Min ; Max	-27.58 ; 19.10	-16.54 ; 15.32	-17.22 ; 0.69
Statistical analysis	E (SE)[(1)]	2.73 (0.48)	4.65 (0.49)	
(S 12911 groups *versus* alendronate)	95%CI[(2)]	[1.67 ; 3.79]	[3.57 ; 5.73]	
	p-value[(3)]	**< 0.001**	**< 0.001**	

Baseline value at the selection, End value at M6 or M12 depending on the time of the second biopsy

(1) estimate (standard error) of S 12911 minus alendronate difference between group means based on a parametric covariance analysis adjusted for baseline value and country

(2) 95% Confidence Interval of the estimate

(3) Multiple comparison p-value (Dunnett's test)

These results were confirmed in the PPS1 and the PPS2.

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Relative change from baseline to last value in the FAS

In the FAS, the decrease in MS/BS (Cn) was lower in the S 12911 groups than in the alendronate group with the following relative changes in MS/BS: -11.4 ± 185.7% in the S 12911 M6 group, -12.7 ± 158.8% in the S 12911 M12 group and -82.3 ± 116.3% in the alendronate group. The differences *versus* alendronate were significant:

- S 12911 M6: E (SE) = 68.7 (23.5), 95%CI = [16.4 ; 121.0], p = 0.007.
- S 12911 M12: E (SE) = 99.8 (23.6), 95%CI = [47.4 ; 152.2], p < 0.001.

Similar results were obtained in the PPS1 and PPS2.

Change from baseline to each visit within S 12911 groups in the FAS

The decreases in MS/BS (Cn) within each S 12911 group were statistically significant from baseline to End: -2.6 ± 5.5% in the S 12911 M6 group (95%CI = [−3.73 ; −1.45], p < 0.001) and −1.7 ± 5.5% in the S 12911 M12 group (95%CI = [−2.89 ; −0.56], p < 0.004).

Within-group change from baseline to last value in patients with a low baseline cancellous MS/BS value the FAS (complementary analysis)

In a subgroup of patients treated with S 12911, with baseline MS/BS value inferior to 5.01% (*i.e.* the median value) representing patients with a low bone turnover (N = 90), the cancellous MS/BS remained stable in the S 12911 M6 group (-0.27 ± 2.90%, p = 0.49) and statistically increased in the S 12911 M12 group (1.13 ± 3.16%, p = 0.036) suggesting an increase in bone formation occurring over M6-M12.

In the subgroup of patients with a baseline MS/BS value superior to the median (5.01%) in the S 12911 group, a decrease was observed both in the S 12911 M6 group: E (SE) = -5.91 (1.07)% and in the S 12911 M12 group: E (SE) = -3.75 (0.83)% (complementary analysis).

Secondary criteria

Other histomorphometry parameters

Bone formation parameters

The dynamic and static bone formation parameters (Cn) decreased from baseline to End in both S 12911 groups, except osteoid maturation time and osteoblast surface/BS in the S 12911 M12 group, and in S 12911 M6 and M12 group for osteoid surface/BS, and osteoid volume/bone volume. The decrease in all parameters was slightly more marked in the S 12911 M6 group than in the S 12911 M12 group.

The mean change from baseline to End in dynamic and static bone formation parameters (Cn) was lower in the S 12911 M6 and M12 groups than in the alendronate group, with a statistically significant difference between the S 12911 groups and the alendronate group (p < 0.001 for all comparisons), except for osteoid maturation time in the S 12911 M6 group (p = 0.23).

The results of endocortical and the sum of endocortical and cancellous parameters showed same trends.

In the subgroup of patients treated with S 12911 having a baseline MS/BS value inferior to the median of 5.01% (N = 90/179 patients), a statistically significant increase from baseline to End was observed in the S 12911 M12 group for BFR/BS (p = 0.031), and activation frequency (p = 0.037). A trend to an increase over time within each S 12911 group was observed for the other parameters (OS/BS, OV/BV, Ob.S/BS), although it did not reach statistical significance.

The between-group difference (S 12911 groups *versus* alendronate group) in the mean change from baseline to End in the main bone formation parameters is summarised in Table hereafter.

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Main bone formation histomorphometric parameters - Changes from baseline to End in the FAS - Between-group comparison (S 12911 groups *versus* alendronate)

Parameters		**S 12911 M6 (N = 90)**	**S 12911 M12 (N = 89)**	**Alendronate (M6/M12) (N = 89)**
Dynamic parameters				
BFR/BS (Cn) (µm3/µm^2/d)	n	76	84	37*
	Mean ± SD	-0.02 ± 0.03	-0.01 ± 0.04	-0.03 ± 0.02
Statistical analysis	Min ; Max	-0.12 ; 0.12	-0.11 ; 0.00	-0.10 ; 0.00
(S 12911 groups *versus* alendronate)	E (SE)[1]	0.02 (0.00)	0.03 (0.00)	
	95% CI[2]	[0.01 ; 0.03]	[0.02 ; 0.04]	
	p value[3]	< **0.001**	< **0.001**	
Static cancellous parameters				
Osteoblast surface/BS (Cn) (%)	n	90	89	89
	Mean ± SD	-0.57 ± 1.99	-0.18 ± 2.22	-1.66 ± 1.74
	Min ; Max	-6.04 ; 3.94	-5.17 ; 6.34	-8.89 ; 0.34
	E (SE)[1]	1.18 (0.20)	1.68 (0.20)	
	95% CI[2]	[0.74 ; 1.61]	[1.24 ; 2.12]	
	p value[3]	< **0.001**	< **0.001**	
Osteoid surface/BS (Cn) (%)	n	90	89	89
	Mean ± SD	0.97 ± 9.74	-1.05 ± 8.69	-4.64 ± 6.88
	Min ; Max	-17.80 ; 31.59	-32.30 ; 24.87	-31.59 ; 16.55
Statistical analysis	E (SE)[1]	5.80 (1.03)	5.24 (1.05)	
(S 12911 groups *versus* alendronate)	95% CI[2]	[3.51 ; 8.09]	[2.91 ; 7.57]	
	p value[3]	< **0.001**	< **0.001**	
Osteoid volume/bone volume (Cn) (%)	n	90	89	89
	Mean ± SD	-0.22 ± 2.08	-0.37 ± 2.26	-1.55 ± 1.59
	Min ; Max	-4.81 ; 9.28	-10.38 ; 8.34	-7.56 ; 2.13
Statistical analysis	E (SE)[1]	1.35 (0.22)	1.51 (0.22)	
(S 12911 groups *versus* alendronate)	95% CI[2]	[0.86 ; 1.83]	[1.01 ; 2.00]	
	p value[3]	< **0.001**	< **0.001**	

1 estimate (standard error) of S 12911 minus alendronate difference between group means based on a parametric covariance analysis adjusted for baseline value and country; 2 95% Confidence Interval of the Estimate;3 corresponding p-value

** When no double-labelling was present, the BFR calculation could not be performed, explaining the low number of reported data.*

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Bone Mineralization parameters

Cancellous and cortical mineral apposition rates (MAR) did not change over time within each S 12911 group from baseline to End, while a decrease was observed in the alendronate group, with a statistically significant between-group difference (cancellous MAR: $p = 0.001$ and $p < 0.001$, in the S 12911 M6 and M12 group, respectively, and cortical MAR: $p = 0.003$ and $p = 0.009$, respectively).

No relevant changes were observed on endocortical and cancellous and endocortical mineral apposition rates whatever the treatment group.

The mineralisation lag time increased over time in all groups, with a statistically significant within-group difference in the S 12911 M6 group ($p = 0.02$), while it was not statistically significant at M12. The mean change over time was lower in the S 12911 groups than in the alendronate, with a statistically significant between-group difference ($p = 0.008$ in the S 12911 M6 group and $p < 0.001$ in the S 12911 M12 group).

In the subgroup of patients treated with S 12911, with baseline MS/BS value inferior to 5.01%, no statistically significant change over time in mineralisation parameters was detected within each S 12911 group.

Bone Resorption parameters

Resorption parameters did not change over time within each S 12911 group, except eroded volume/bone volume that increased in the M6 group ($p = 0.04$), while a decrease was observed in the alendronate group. A statistically significant difference between the S 12911 groups and the alendronate group was found for the cancellous eroded surface/BS and eroded volume/bone volume ($p < 0.001$ for both parameters), and for the cancellous osteoclast parameters between the S 12911 group at M12 and the alendronate group ($p = 0.009$ for osteoclast number/BS and $p = 0.040$ for osteoclast surface/BS).

The results showed same trends for those relative to endocortical and the sum of endocortical and cancellous localisation.

In the subgroup of patients treated with S 12911, with baseline MS/BS value inferior to 5.01%, no statistically significant change over time in bone resorption parameters was detected within each S 12911 group.

Bone Structure parameters

For trabecular parameters, there was a decrease over time within the S 12911 M12 group in trabecular thickness ($p = 0.024$) and bone volume/tissue volume ($p = 0.011$), a decrease in wall thickness in the S 12911 M6 group ($p = 0.007$), an increase in the trabecular separation in the S 12911 M6 group ($p = 0.035$) and M12 group ($p = 0.034$). However, no statistical significant between-group difference was detected between the S 12911 groups and the alendronate group.

For cortical parameters, no within S 12911 group change over time was detected for cortical thickness and porosity. As regards cortical porosity, there was a decrease over time in the alendronate group, with a statistically significant difference with S 12911 groups:

- S 12911 M6 *versus* alendronate: E (SE) = 1.18 (0.50), 95% CI = [0.08 ; 2.29], $p = 0.034$.
- S 12911 M12 *versus* alendronate: E (SE) = 1.17 (0.50), 95% CI = [0.05 ; 2.28], $p = 0.039$.

In the subgroup of patients treated with S 12911, with baseline MS/BS value inferior to 5.01%, no statistically significant change over time in bone structure parameters was detected within each S 12911group.

- **Microradiography and microCT**

No relevant differences over time nor between-groups were observed.

- **Lumbar, total hip and femoral neck BMD** increased from baseline to End in the S 12911 group and in the alendronate group. The between-group differences were not statistically significant. The relatives changes from baseline to last value were:
  - Mean lumbar L2-L4 BMD: 4.7 ± 5.2% in the S 12911 group and 5.8 ± 4.3% in the alendronate group.
  - Mean femoral neck BMD: 2.6 ± 3.8% and 2.7 ± 2.9%, respectively.
  - Mean total hip BMD: 3.4 ± 3.3% and 3.0 ± 2.4%, respectively.

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

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

Mean changes from baseline to last value in **b-ALP** were –0.82 ± 3.50 ng/mL in the S 12911 group and –7.16 ± 4.62 ng/mL in the alendronate group. The difference between groups was significant: E (SE) = 6.44 (0.42), 95%CI = [5.62 ; 7.27], p < 0.001.

Mean changes from baseline to last value in **s-CTX** were –0.05 ± 0.21 ng/mL in the S 12911 group and -0.40 ± 0.23 ng/mL in the alendronate group. The difference between groups was significant: E (SE) = 0.36 (0.02), 95%CI = [0.32 ; 0.41], p < 0.001.

Mean changes from baseline to last value in **PINP** were –6.22 ± 15.60 µg/l in the S 12911 group and -37.12 ± 20.99 µg/l in the alendronate group. The difference between groups was significant: E (SE) = 30.64 (1.79), 95%CI = [27.12 ; 34.16], p < 0.001

There was no relevant difference between groups in mean changes from baseline to last value in OPG.

SAFETY RESULTS

Safety results are summarised below:

Main safety results in the Safety Set

		S 12911 (N = 255)	**Alendronate (N = 132)**
Number of patients with at least:			
one emergent adverse event	n (%)	175 (68.6)	86 (65.2)
one treatment-related emergent adverse event	n (%)	48 (18.8)	27 (20.5)
one emergent adverse event leading to treatment discontinuation	n (%)	19 (7.5)	4 (3.0)
one serious emergent adverse event	n (%)	18 (7.1)	4 (3.0)
one serious treatment-related emergent adverse event	n (%)	1 (0.4)	-
Patients who died	n (%)	2 (0.8)	-
Number of patients with at least one biological abnormality			
emergent blood calcium value < lower limit of reference range	n (%)	50 (21.6)	12 (9.4)
emergent blood phosphorus value > upper limit of reference range	n (%)	24 (10.3)	4 (3.1)
emergent CPK value > upper limit of reference range	n (%)	25 (10.7)	5 (3.9)

n number of patients

% calculated as percentage of patients in the Safety Set in each treatment group

The frequency of patients who reported at least one **emergent adverse event** was close in both treatment groups: 175 patients (68.6%) in the S 12911 group and 86 patients (65.2%) in the alendronate group.

The most frequently affected system organ classes were infections and infestations (28.2% of the patients in the S 12911 group *versus* 25.8% in the alendronate group), gastrointestinal disorders (23.5% *versus* 21.2%, respectively) and musculoskeletal and connective tissue disorders, with a higher frequency in the S 12911 group than in the alendronate group (22.0% *versus* 16.7%, respectively).

The most commonly reported emergent adverse events in the S 12911 group were procedural pain with a higher frequency reported in the S 12911 group than in the alendronate group (10.2% in the S 12911 group *versus* 7.6% in the alendronate group), back pain (6.3% versus 6.1%, respectively) and nasopharyngitis (5.1% *versus* 3.0%, respectively). Most of the adverse events reported with S 12911 group were listed.

Most emergent adverse events were rated as mild or moderate (95.3% of the events). Severe emergent adverse events were more frequently reported in the S 12911 group than in the alendronate group: 15 patients (5.9%) in the S 12911 group *versus* 3 patients (2.3%) in the alendronate group.

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

The difference between the two groups in terms of frequency was mainly due to injury, poisoning and procedural complications (2.0% *versus* none, respectively) including fall (2 patients 0.8% *versus* none, respectively). None of the severe emergent adverse events was considered as treatment-related according to the investigator except muscular pain in one patient in the S 12911 group.

Treatment-related emergent adverse events were reported in 75 patients: 48 patients (18.8%) in the S 12911 group and 27 patients (20.5%) in the alendronate group. The system organ classes most commonly affected in both groups were gastrointestinal disorders (11.8% of the patients in the S 12911 group *versus* 13.6% in the alendronate group) and musculoskeletal and connective tissue disorders (2.7% *versus* 3.0%, respectively). Most of the emergent treatment-related adverse events observed under S 12911 treatment corresponded to listed events.

Emergent adverse events leading to **premature treatment discontinuation** were more frequently reported in the S 12911 group than in the alendronate group: 19 patients (7.5%) in the S 12911 group and 4 patients (3.0%) in the alendronate group. These events concerned mainly gastrointestinal disorders (3.1% *versus* 2.3%, respectively) and musculoskeletal and connective tissue disorders (1.6% *versus* 0.8%, respectively).

Serious emergent adverse events were reported in 22 patients: 18 patients (7.1%) in the S 12911 group and 4 patients (3.0%) in the alendronate group. The most frequently affected system organ classes were injury, poisoning and procedural complications (6 patients (2.4%), including 5 having fracture) in the S 12911 group *versus* none in the alendronate group) and neoplasms benign, malignant and unspecified (0.8% in both groups) and nervous system disorders (0.8% in both groups). The only preferred term reported twice in the S 12911 group was wrist fracture (2 patients, 0.8% in the S 129111 group *versus* none in the alendronate group). The 7 fractures occuring in 5 patients in the S 12911 group (*versus* none in the alendronate group), were due to falls. One serious emergent rash papular in the S 12911 group was considered as treatment-related according to the investigator. This event, that occuured 49 days after the first study drug intake, led to study drug withdrawal and was recovered one month later with a corticosteroid local treatment. The patient had no systemic symptoms nor eosinophilia associated with the papular rash.

Death

Two patients in the S 12911 group died during the study: one from cervix carcinoma and one from traumatic brain injury. Deaths were considered unrelated to the study treatment according to the investigator.

Laboratory tests

Neither clinically relevant changes, nor differences between groups were detected for biochemistry parameters. As expected for CPK, there was a slight increase from baseline (104.2 ± 63.1 IU/L) to last value under treatment (116.4 ± 71.1 IU/L) in the S 12911 group with a mean change ± SD = 12.2 ± 50.4 IU/L, whereas it remained stable in the alendronate group (mean ± SD = -1.5 ± 40.2 IU/L). Blood calcium decreased in both treatment groups from baseline to last value under treatment: -0.052 ± 0.102 IU/L in the S 12911 group and -0.033 ± 0.125 IU/L in the alendronate group. In the S 12911 group, 25 patients (10.7%) had a high out-of-reference-range calcium value as compared to 5 patients (3.9%) in the alendronate group. In the S 12911 group, 50 patients (21.6%) had low out-of-reference-range calcium value as compared to 12 patients (9.4%) in the alendronate group. Blood phosphorus was increased with S 12911: 0.067 ± 0.172 mmol/L *versus* -0.104 ± 0.182 mmol/L in the alendronate group. A total of 28 patients had high out-of-reference-range phosphorus value: 24 patients (10.3%) in the S 12911 group and 4 patients (3.1%) in the alendronate group.

Emergent PCSA values were reported in the S 12911 group for phosphorus (high values) in 19 patients (8.2%), and calcium (low value) in 1 patient (0.4%). In the alendronate group emergent PCSA values were reported for phosphorus (2 high and 2 low values) in 2 patients each one (1.6%), and CPK (high value) in one patient (0.8%).

No clinically relevant change over time or between-group difference were detected for haematological parameters except for high out-of-reference-range value of eosinophils more frequently reported in the S 12911 group than in the alendronate group (14 patients (6.0%) *versus* 1 patient (0.8%), respectively).

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Low PCSA values were reported in 3 patients in the S 12911 group: 2 patients for white blood cells and 2 patients for neutrophils (1 patient having PCSA value for both parameters), and 6 patients in the alendronate group: 1 patient for white blood cells, 5 patients for neutrophils, and 1 patient for lymphocytes (1 patient having PCSA for white blood cells and lymphocytes parameter).

Vital signs

Neither clinically relevant change, nor difference between groups was detected for vitals signs.

Bone sample quality

Most patients had a complete biopsy: 248 patients (97.3%) in the S 12911 group and 127 (96.2%) in the alendronate group at selection and 188 patients (90.8%) and 101 patients (87.1%), respectively at the end of the study. No patients had osteomalacia and no mineralization defect was observed in both groups. However mineralization apposition rate tended to decrease in the alendronate group, and mineralization lag time increased more in the alendronate group. The strong inhibition of bone formation obtained with alendronate was not observed with S 12911.

Bone strontium content

Bone strontium content ratio was 0.34 ± 0.23% at M6 in the S 12911 M6 group and 0.61 ± 0.1% at M12 in the S 12911 M12 group.

CONCLUSION

This study, conducted in 387 postmenopausal women with osteoporosis, aimed at evaluating the effects of 6 and 12 months treatment with S 12911 in comparison with alendronate on bone formation assessed by histomorphometry on transiliac paired biopsies. Results showed that the decrease in mean cancellous mineralizing surfaces to bone surface (Cn.MS/BS), a bone formation parameter, was significantly lower in the S 12911 M6 and M12 groups than in the alendronate group ($p < 0.001$ in each S 12911 group *versus* alendronate).

Most of the other bone formation parameters decreased over time in all treatment groups but with a lower magnitude in the S 12911 groups than in the alendronate group, with a statistically significant between-group difference ($p < 0.001$ in each S 12911 group *versus* alendronate). Mineralisation parameters (cancellous and cortical mineral apposition rates) did not change over time within each S 12911 group, while a decrease was observed in the alendronate group, with a statistically significant between-group difference. Bone resorption parameters were decreased over time with alendronate, while no statistically significant change was detected within each S 12911 group. No statistically significant between-group difference was detected for structure parameters, except for cortical porosity parameter. No within group change in cortical porosity was detected in the S 12911 group, while a decrease was observed in the alendronate group.

In a subgroup of patients treated with S 12911 having a low baseline bone formation (Cn.MS/BS < median value of 5.01%, N = 90 patients, complementary analysis), main bone formation parameters were significantly increased from baseline to End in the S 12911 M12 group. Other formation parameters also tended to increase. No significant changes in resorption parameters were detected in this subgroup. These results suggest an increase in bone formation after 12 months of treatment with S 12911 in patients having a low baseline bone turnover, and a decrease in the other patients.

The increase in lumbar, femoral neck and total hip BMD were consistent with that previously observed in large SOTI and TROPOS Phase III studies. The bone markers analysis showed that bone formation was maintained with S 12911 while a decrease was observed with alendronate. Safety results were in accordance with the known profile of S 12911.

Overall, the strong inhibition of bone formation obtained with alendronate was not observed with S 12911, suggesting the maintenance of bone turnover and physiology under S 12911 treatment.

Date of the report: 26 March 2012