I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**Clinical Study Report Synopsis**
Study title	**A double-blind, multicentric, multinational randomised study to assess the effects of two years administration of 2g per day of strontium ranelate *versus* alendronate 70mg per week in women with postmenopausal osteoporosis on bone geometry and bone strength measured by peripheral Quantitative Computed Tomography (p-QCT).**
Study drug	**S 12911**
Studied indication	**Treatment of post-menopausal osteoporosis**
Development phase	**Phase III**
Protocol code	**CL3-12911-030**
Study initiation date	**19 February 2008**
Study completion date	**07 April 2011**
Main coordinator	[redacted] **GERMANY**
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 3 April 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, multicentric, multinational randomised study to assess the effects of two years administration of 2 g per day of strontium ranelate *versus* alendronate 70 mg per week in women with postmenopausal osteoporosis on bone geometry and bone strength measured by peripheral-Quantitative Computed Tomography (pQCT).
Protocol No.: CL3-12911-030

International Coordinator: [redacted] Germany.
National Coordinators: [redacted], Italy), [redacted], Sweden) and [redacted] Greece).

Study centre:
Multicentric study (9 active centres, 4 countries, 189 patients included).
Germany (3 centres, 117 patients), Greece (1 centre, 3 patients), Italy (3 centres, 44 patients), Sweden (2 centres, 25 patients).

Publication: Abstracts (one-year analysis):

- Felsenberg D., *et al.* Superior effects of strontium ranelate compared to alendronate on bone mass and strength parameters at the tibia in women with post menopausal osteoporosis. Osteoporosis Int 2011;22(suppl. 1):S102. Ann Rheum Dis 2011;70(Suppl3): 137.

Studied period: Initiation date: 19 February 2008 Completion date: 7 April 2011	**Phase of development of the study:** III

Objective:
Initially, this exploratory study was designated to evaluate the effects of a two-year administration of 2 g per day of strontium ranelate *versus* alendronate 70 mg per week in women with postmenopausal osteoporosis on bone geometrical parameters and bone strength indexes measured by pQCT.
Amendment No. 3 modified the objective of the study from an exploratory to a comparative one, the objective of this study was then to compare the effects of a two-year administration of 2 g per day of strontium ranelate *versus* alendronate 70 mg per week in women with postmenopausal osteoporosis on cortical thickness, bone geometrical parameters and bone strength indexes measured by pQCT.

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

Number of patients:
Planned: initially, 80 patients (40 in each treatment group); following Amendment No. 3, 148 patients (74 patients in each treatment group).
Included: 189 patients (93 patients in the S 12911 group and 96 patients in the alendronate group).

Diagnosis and main criteria for inclusion:
Postmenopausal (for at least 5 years) women ≥ 50 years old with diagnosed osteoporosis (defined as T-score measured by Dual-energy X-ray Absorptiometry (DXA) ≤ -2.5 at either the femoral neck or the total hip or the lumbar levels (L1-L4)).

Study drug:
One S 12911 2 g sachet once a day at bedtime associated with elemental calcium 500 mg/day and vitamin D 400 IU/ day taken at lunchtime.
Batch No.: L0019406 - L0023867 - L0025395 - L0026544 - L0026826 - L0027560
(+ placebo, 1 capsule per week, to maintain the double-blind)

Reference product:
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.
(+ placebo, 1 sachet per day, to maintain the double-blind)

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Duration of treatment:
Two years

Criteria for evaluation:

Efficacy measurements:

Main criterion: cortical thickness for tibia (14%, *i.e.* the site of measurement at 14% of the distal end of the tibia) by pQCT at M000, M006, M012, M018 and M024 visits.

Secondary criteria:

- Other bone geometry and bone strength parameters assessed for tibia and radius by pQCT at M000, M006, M012, M018 and M024 visits.
- Lumbar, femoral neck and total hip Bone Mineral Density (BMD) by DXA at selection, M012 and M024 visits.
- Bone markers: Bone Alkaline Phosphatase (b-ALP) and serum CTX (s-CTX) at selection, M006, M012, M018 and M024 visits.

The assessments of pQCT parameters, BMD by DXA and bone markers were centralised.

Safety measurements:

- Adverse events assessed at each visit
- Laboratory safety parameters: calcium was assessed at each visit from selection to M024 except M000. Full blood cell count, blood creatinine and CPK (total and isoenzymes if CPK above normal ranges of laboratory) were assessed at selection, M012 and M024 visits. Prothrombin time, sodium, chloride, ASAT, ALAT, GGT and alkaline phosphatase were assessed only at selection visit.
- Vital signs: weight, height, systolic and diastolic blood pressure and heart rate assessed at each visit except for weight and height only assessed at selection, M012 and M024 visits.

Drug concentration:

- Serum levels of strontium were assessed by high frequency inductively coupled plasma atomic emission spectrophotometry (ICP-AES) at each visit.

Statistical methods:

Efficacy analysis:

The Full Analysis Set (FAS, main efficacy analysis set) was defined as all randomised patients who took at least one dose of study treatment (capsule or sachet) and who have one available (*i.e.* not missing) baseline evaluation and at least one available post-baseline evaluation for Cortical thickness for tibia (14%).

The SubFAS was defined as patients of the FAS whose last post-baseline available evaluation was M018 or M024.

Two subgroups were also identified for the analyses:

- Subgroup 1: Patients with a T-score at selection ≤ -2.5 at either femoral neck or total hip (yes/no).
- Subgroup 2: Patients with a lumbar T-score at selection ≤ -2.5 (yes/no).

Primary efficacy criterion: cortical thickness for tibia (14%)

Main analysis:

The main analytical approach was the relative change from baseline to last reliable post-baseline value over 24 months (END). The comparison between S 12911 and alendronate was performed in the FAS using a general linear model studying treatment effect with centre as fixed factor. Estimate of the difference between adjusted group means, its Standard Error (SE), its two-sided 95% Confidence Interval (CI) and the associated p-value were provided.

Note: Centres with less than 5 patients in the analysis were pooled with the biggest centre of the same country. The unique centre in Greece was pooled with the biggest centre in Italy (closest country in terms of patients' characteristics).

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Statistical methods (Cont'd):

Sensitivity analyses:

- Treatment groups were compared on the relative change from baseline to END using a Mann-Whitney-Wilcoxon test (non-parametric approach without adjustment).
- The same analyses (parametric and non-parametric analyses) were performed in the SubFAS and in each subgroup of the FAS.

Note: for parametric analysis in the subgroups of FAS, the analysis was adjusted on country as fixed factor instead of centre. For this analysis, Greece and Italy were pooled.

Secondary analyses:

- The treatment effect on the change (absolute) from baseline to each visit and to last post-baseline value was estimated using a general linear model adjusted on baseline and centre (fixed factor) as covariates. A non-parametric analysis as defined above was also performed considering the changes (absolute) from baseline to each visit and to last post-baseline value.
- The treatment effect on the relative change from baseline to each visit was estimated using the same analyses (parametric and non-parametric analyses) as defined for the relative change from baseline to last post-baseline value.
- The within-group change over time from baseline to each visit and to END was tested using a two-sided paired Student's t test and a Wilcoxon signed-rank test (non-parametric approach).

Secondary efficacy criteria: other geometrical and bone strength parameters, bone markers, BMD

The same analyses as defined above for the main criterion were performed on all secondary efficacy criteria.

Safety analyses

Adverse events, laboratory parameters and vital signs were assessed through descriptive statistics in the Safety Set.

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 189 postmenopausal women with osteoporosis were included in the study and randomly assigned to one of the 2 groups: 93 patients in the S 12911 group and 96 patients in the alendronate group. A well-balanced distribution was achieved. The disposition of patients by group and overall is presented in the following table.

Disposition of patients by group

Status	**S 12911**	**Alendronate**	**All**
Included (randomised)	**93**	**96**	**189**
Lost to follow-up	-	-	-
Withdrawn due to	**31**	**33**	**64**
Adverse events	18	18	36
Non-medical reason	13	13	26
Protocol deviation	-	2	2
Completed	**62**	**63**	**125**
Full Analysis Set (FAS)	77 (82.8) [a]	76 (79.2) [a]	153 (81.0) [a]
Sub Full Analysis Set (SubFAS)	66 (71.0) [a]	63 (65.6) [a]	129 (68.3) [a]
FAS- Subgroups			
Patients with a T-score at selection ≤ -2.5 at either target femoral neck or the target total hip (subgroup 1)	33 (42.9) [b]	33 (43.4) [b]	66 (43.1) [b]
Patients with a lumbar T-score at selection ≤ -2.5 (subgroup 2)	63 (81.8) [b]	57 (75.0) [b]	120 (78.4) [b]
Safety set	91	95	186

[a]: *% of the Randomised set*
[b]: *% of the FAS*

At selection, patients were aged from 52 to 83 years old with a mean ± SD of 67.7 ± 5.9 years old. The mean time since menopause was 19.2 ± 7.2 years. Mean BMI was 24.4 ± 2.9 kg/m².
No relevant difference between groups was noted for demographic data, gynaecological status and vital signs.

Mean time since diagnosis of osteoporosis was 24.0 ± 51.3 months with at least 50% of the patients diagnosed the day of selection (median = 0 month in both groups). A total of 35 patients (18.6%) reported at least one previous osteoporotic fracture: 10 patients (5.3%) reported at least one previous osteoporotic vertebral fracture and 29 patients (15.4%) at least one osteoporotic non-vertebral fracture, without relevant difference between groups. In all, 47 patients (24.9%) had taken at least one previous treatment for osteoporosis and/or likely to interfere with bone metabolism, mainly mineral supplements (13.2%, mainly calcium + vitamin D and calcium) and drugs for treatment of bone diseases (10.6%, mainly alendronate sodium); a slight difference between groups was observed for drugs for treatment of bone diseases (14.0% in the S 12911 group *versus* 7.3% in the alendronate group).

No relevant difference between groups was observed regarding risk factors (smoking habits, alcohol consumption, mobility and physical activity).
The mean lumbar L1-L4 BMD was 0.805 ± 0.073 g/cm², the mean femoral neck BMD 0.722 ± 0.096 g/cm² and the mean total hip BMD 0.759 ± 0.094 g/cm². The corresponding mean BMD T-scores were -3.13 ± 0.61 - 2.27 ± 0.69 and -1.98 ± 0.75, respectively (according to Lunar caucasian references).

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

The mean baseline values of bone markers were 0.634 ± 0.252 ng/mL for serum CTX and 15.63 ± 5.46 ng/mL for bone alkaline phosphatase.

No relevant between-group difference was observed for the baseline BMD values and bone markers.

The mean baseline value of cortical thickness 14% for tibia (main efficacy criterion) was 1.830 ± 0.340 mm in the S 12911 group and 1.779 ± 0.357 mm in the alendronate group: no relevant between-group difference was observed for geometrical and bone strength parameters.

In the RS, most of patients (96.8%) reported at least one medical history other than osteoporosis, mainly hypertension (30.7%), osteoarthitis (22.8%) and hypercholesterolaemia (22.2%). Regarding medical histories, the main differences between groups were observed for eye disorders (32.3% in the S 12911 group *versus* 9.4% in the alendronate group) with cataract (20.4% *versus* 5.2%), gastrointestinal disorders (17.2% *versus* 29.2%) and vascular disorders (34.4% *versus* 45.8%) with varicose veins (7.5% *versus* 16.7%) as well as for osteoarthritis (18.3% *versus* 27.1%).

Overall, 93.1% of the patients took at least one concomitant treatment at inclusion, mainly mineral supplements (82.5%) and vitamins (82.0%): the main differences between S 12911 and alendronate groups were observed for ophthalmologicals (11.8% *versus* 3.1%) and antithrombotic agents (4.3% *versus* 11.5%).

During the study, 97.9% of the patients took at least one concomitant treatment: the main differences between groups were observed for ophthalmologicals (19.4% in the S 12911 group *versus* 8.3% in the alendronate group), drugs for acid related disorders (8.6% *versus* 16.7%, respectively) and antihistamines for systemic use (3.2% *versus* 10.4%, respectively).

Baseline characteristics in the FAS (N = 153, 81.0% of the RS) and SubFAS (N = 129, 68.3% of the RS) were close to those in the RS.

In the Safety Set, the mean treatment duration for active treatment was 18.6 ± 8.9 months for S 12911 and 17.6 ± 9.3 months for alendronate. Regarding exposure to active treatment, patients were slightly more exposed to S 12911 at least 18 months (71.4%) than to alendronate (63.2%).

In the FAS, the mean treatment duration was 21.6 ± 5.7 months for S 12911 and 21.0 ± 6.3 months for alendronate. The global compliance to active treatment was good as 88.3% and 92.1% of patients had a compliance > 80% for S 12911 and alendronate, respectively.

The strontium blood levels in the S 12911 group [redacted]

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EFFICACY RESULTS

- **Primary assessment criterion: cortical thickness (14%) for tibia**

In the FAS, cortical thickness (14%) for tibia slightly increased from baseline to END in both groups with a relative change of 0.70 ± 2.46% in the S 12911 group *versus* 0.36 ± 2.73% in the alendronate group. The between-group difference estimated at 0.35% was not statistically significant (main analysis, see the following Table).

Cortical thickness for tibia (14%) – Relative change from baseline to END
Comparison between treatment groups - M000-M024 period - FAS

Cortical thickness (14%) (mm)		**S 12911 (N = 77)**	**Alendronate (N = 76)**
Baseline	n	77	76
	Mean ± SD	1.841 ± 0.335	1.781 ± 0.366
	Min ; Max	1.06 ; 2.58	1.00 ; 2.92
END	n	77	76
	Mean ± SD	1.854 ± 0.341	1.790 ± 0.380
	Min ; Max	1.08 ; 2.64	0.92 ; 2.96
Relative change from baseline to END (%)	n	77	76
	Mean ± SD	0.70 ± 2.46	0.36 ± 2.73
	Min ; Max	-6.2 ; 6.4	-7.7 ; 5.7
Statistical analysis			
Main analysis: parametric approach	E (SE) (1.1)	0.35 (0.42)	
	95% CI (2)	[-0.49; 1.18]	
	p-value (3.1)	0.4125	
Sensitivity analysis: non-parametric approach	E (1.2)	0.15	
	95% CI (2)	[-0.60; 0.93]	
	p-value (3.2)	0.6681	

Two-sided type I error rate: 0.05
(1.1) Estimate (Standard Error) of the difference between centre adjusted treatment group means: Strontium ranelate minus Alendronate
(1.2) Estimate of Hodges-Lehmann for the difference between treatment group means: Strontium ranelate minus Alendronate;(2) 95% Confidence interval of the estimate;(3.1) General linear model with centre as fixed factor;(3.2) Mann-Whitney-Wilcoxon test

In the subFAS and in the subgroups 1 and 2 of the FAS, cortical thickness (14%) for tibia slightly increased from baseline to END in both S 12911 and alendronate groups (except in the alendronate group for the subgroup 1) without statistically significant between-group difference in relative change from baseline to END.

In the FAS, the corresponding absolute mean changes of cortical thickness 14% from baseline to END, were 0.013 ± 0.042 mm in the S 12911 group *versus* 0.009 ± 0.042 mm in the alendronate group without statistically significant between-group difference [E(SE) = 0.003 (0.007) mm]. The increase from baseline to END was statistically significant in the S 12911 group with both parametric and non-parametric approaches (p = 0.0095 and 0.0093, respectively); in the alendronate group, the increase was close to the statistical significance with the parametric approach and statistically significant with the non-parametric approach (p = 0.0622 and 0.0390, respectively).

The estimated between-group differences on the relative change from baseline to each visit (*i.e.* M006, M012, M018 and M024) were not statistically significant.

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EFFICACY RESULTS (Cont'd)

- **Secondary assessment criteria**: geometrical and bone strength parameters for tibia and radius, bone markers and BMD

Geometrical and bone strength parameters

Geometrical and bone strength parameters for tibia

Relative changes from baseline to END in geometrical and bone strength parameters for tibia are presented in the following Table.

Geometrical and bone strength parameters - Tibia - Relative changes (%) from baseline to END - M000-M024 period – FAS

	Relative changes (%) from baseline to END		**Between-group difference** (parametric approach)		
	S 12911 (N = 77)	**Alendronate (N = 76)**	E(SE)[1]	95%CI[2]	p value[3]
Cortical thickness (4%) (mm)	20.87 ± 21.58	8.12 ± 14.29	12.57 (2.95)	[6.74; 18.40]	**<0.0001**
Periostal circumference (4%) (mm)	0.05 ± 0.36	0.04 ± 0.44	0.02 (0.07)	[-0.11; 0.15]	0.7986
Endostal circumference (4%) (mm)	-0.35 ± 0.60	-0.09 ± 0.56	-0.25 (0.09)	[-0.44; -0.06]	**0.0090**
Total BMD (4%) (mg/ccm)	3.23 ± 2.88	1.60 ± 2.60	1.66 (0.45)	[0.78; 2.54]	**0.0003**
Trabecular BMD (4%) (mg/ccm)	2.24 ± 2.52	1.25 ± 2.74	1.01 (0.42)	[0.18; 1.84]	**0.0173**
Total bone content (4%) (mg/mm)	3.33 ± 2.77	1.69 ± 2.62	1.69 (0.43)	[0.83; 2.54]	**0.0001**
Trabecular content (4%) (mg/mm)	2.34 ± 2.53	1.34 ± 2.92	1.04 (0.43)	[0.19; 1.90]	**0.0167**
Total cross sectional area (4%) (mm^2)	0.10 ± 0.72	0.09 ± 0.88	0.03 (0.13)	[-0.22; 0.29]	0.8030
Trabecular cross sectional area (4%) (mm^2)	0.10 ± 0.72	0.09 ± 0.88	0.03 (0.13)	[-0.23; 0.29]	0.8054
Periostal circumference (14%) (mm)	0.15 ± 0.43	0.15 ± 0.40	0.00 (0.07)	[-0.13; 0.13]	0.9832
Endostal circumference (14%) (mm)	-0.02 ± 0.79	0.10 ± 0.71	-0.13 (0.12)	[-0.37; 0.11]	0.2976
Cortical BMD (14%) (mg/ccm)	0.66 ± 1.03	0.35 ± 1.00	0.34 (0.16)	[0.02; 0.65]	**0.0366**
Cortical content (14%) (mg/mm)	1.43 ± 2.89	0.71 ± 3.08	0.75 (0.48)	[-0.20; 1.69]	0.1206
Cortical cross section area (14%) (mm^2)	1.00 ± 1.73	0.50 ± 1.90	0.50 (0.30)	[-0.09; 1.08]	0.0952
Moment of inertia (14%) (mm^4)	1.15 ± 1.58	0.50 ± 1.81	0.66 (0.27)	[0.12; 1.20]	**0.0173**
Section modulus (14%) (mm^3)	0.68 ± 1.77	-0.13 ± 2.22	0.82 (0.32)	[0.18; 1.46]	**0.0125**
Density weighted moment of inertia (14%) (mm^4)	1.74 ± 2.12	0.85 ± 2.40	0.92 (0.36)	[0.21; 1.63]	**0.0114**
Strength strain index (14%) (mm^3)	1.31 ± 2.41	0.09 ± 2.27	1.24 (0.37)	[0.51; 1.98]	**0.0011**
Cortical thickness (38%) (mm)	-0.23 ± 2.50	-0.09 ± 1.39	-0.10 (0.33)	[-0.76; 0.55]	0.7511
Periostal circumference (38%) (mm)	1.25 ± 1.60	1.31 ± 1.98	-0.08 (0.27)	[-0.61; 0.44]	0.7618
Endostal circumference (38%) (mm)	3.58 ± 4.81	3.55 ± 5.86	-0.06 (0.78)	[-1.60; 1.49]	0.9422
Cortical BMD (38%) (mg/ccm)	1.14 ± 1.21	0.54 ± 1.13	0.60 (0.17)	[0.26; 0.94]	**0.0006**
Cortical content (38%) (mg/mm)	1.29 ± 2.56	0.79 ± 1.86	0.56 (0.35)	[-0.14; 1.26]	0.1183
Cortical cross section area (38%) (mm^2)	0.09 ± 1.67	0.31 ± 1.13	-0.20 (0.23)	[-0.65; 0.25]	0.3864
Moment of inertia (38%) (mm^4)	0.89 ± 1.79	0.85 ± 1.66	0.10 (0.26)	[-0.41; 0.62]	0.6948
Section modulus (38%) (mm^3)	0.66 ± 1.75	0.72 ± 2.00	0.02 (0.30)	[-0.58; 0.61]	0.9548
Density weighted moment of inertia (38%) (mm^4)	2.23 ± 2.30	1.46 ± 1.95	0.85 (0.33)	[0.19; 1.51]	**0.0114**
Strength strain index (38%) (mm^3)	1.83 ± 2.41	1.27 ± 2.21	0.65 (0.37)	[-0.08; 1.38]	0.0810
Cortical thickness (66%) (mm)	-0.50 ± 2.27	-0.48 ± 2.47	-0.03 (0.37)	[-0.76; 0.71]	0.9410
Periostal circumference (66%) (mm)	5.20 ± 8.07	5.05 ± 6.42	-0.07 (1.10)	[-2.25; 2.11]	0.9486
Endostal circumference (66%) (mm)	9.54 ± 14.56	9.14 ± 11.67	-0.05 (1.99)	[-3.98; 3.88]	0.9808
Cortical BMD (66%) (mg/ccm)	1.02 ± 1.12	0.46 ± 0.99	0.58 (0.16)	[0.27; 0.89]	**0.0003**
Cortical content (66%) (mg/mm)	1.01 ± 2.52	0.41 ± 2.24	0.62 (0.37)	[-0.10; 1.34]	0.0919
Cortical cross section area (66%) (mm^2)	0.15 ± 1.40	0.24 ± 1.07	-0.08 (0.20)	[-0.47; 0.31]	0.6801
Moment of inertia (66%) (mm^4)	1.16 ± 1.74	1.12 ± 2.75	0.09 (0.36)	[-0.61; 0.79]	0.8035
Section modulus (66%) (mm^3)	0.86 ± 1.85	0.63 ± 2.22	0.23 (0.32)	[-0.41; 0.87]	0.4818
Density weighted moment of inertia (66%) (mm^4)	2.17 ± 2.26	1.49 ± 2.37	0.74 (0.36)	[0.02; 1.46]	**0.0428**
Strength strain index (66%) (mm^3)	1.99 ± 2.31	0.78 ± 2.10	1.24 (0.35)	[0.56; 1.93]	**0.0005**
Muscle CSA (66%) (mm^2)	-0.07 ± 4.94	0.84 ± 4.83	-1.02 (0.80)	[-2.59; 0.56]	0.2035

[1] *Estimate (Standard Error) of the difference between centre adjusted treatment group means: Strontium ranelate minus Alendronate;* [2] *95% Confidence interval of the estimate;* [3] *General linear model with centre as fixed factor*

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EFFICACY RESULTS (Cont'd)

Among the analyses performed on geometrical and bone strength parameters which showed a statistically significant between-group difference on the relative change from baseline to END in the FAS, it was interesting to underline the following points:

Total BMD, trabecular BMD, total bone content and trabecular content at the ultra distal tibia (4%) assessed by pQCT increased in both S 12911 and alendronate groups with a statistically significant between-group difference in favour of S 12911 for the 4 parameters.

Regarding bone strength parameters for tibia, moment of inertia, section modulus, density weighted moment of inertia and strength strain index (all increased), a statistically significant effect of S 12911 *versus* alendronate was observed at the distal site (14%), considering the relative change from baseline to END.

Considering the less distal sites of measurement, a statistically significant between-group difference in favour of S 12911 in relative change from baseline to END was observed for density weighted moment of inertia at 38% and 66% as well as for strength strain index at 66%.

Geometrical and bone strength parameters for radius

A statistically significant between-group difference in favour of S 12911 was noteworthy observed in the FAS for total BMD (4%) and total bone content (4%) for radius on the relative changes from baseline to END.

Bone markers

Analysis of **bone markers** in the FAS, showed the following results:

- Mean CTX (marker of bone resorption) values decreased from baseline to END in both groups: -1.59 ± 33.62 % in the S 12911 group and -48.60 ± 29.11% in the alendronate group with a statistically significant between-group difference in favour of alendronate ($p < 0.0001$).
- Mean bone alkaline phosphatase (marker of bone formation) values increased from baseline to END in the S 12911 group (17.63 ± 37.93%) whereas a decrease was observed in the alendronate group (-27.13 ± 25.72%) with a statistically significant between-group difference in favour of S 12911 ($p < 0.0001$).

L1-L4 lumbar, femoral neck and total hip BMD

In the FAS, the mean increase (absolute change) observed from baseline to END in L1-L4 lumbar, femoral neck and total hip **BMD** assessed by DXA was statistically significant in both S 12911 and alendronate groups. Relative changes were the following:

- L1-L4 lumbar BMD: 8.5 ± 6.0 % *versus* 6.8 ± 5.6%, respectively.
- Femoral neck BMD: 5.4 ± 5.7 % *versus* 3.8 ± 4.6%, respectively.
- Total hip BMD: 5.7 ± 6.6 % *versus* 2.6 ± 3.6%, respectively.

The between-group difference was statistically significant in favour of S 12911 for the L1-L4 lumbar ($p = 0.0463$) and the total hip ($p = 0.0002$).

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SAFETY RESULTS

Main safety results are summarised in the table below.

Main safety results

		S 12911 (N = 91)	**Alendronate (N = 95)**
Patients having reported at least			
one emergent adverse event	n (%)	81 (89.0)	79 (83.2)
one treatment-related emergent adverse event	n (%)	27 (29.7)	28 (29.5)
Patients having experienced at least			
one non-fatal serious emergent adverse event	n (%)	14 (15.4)	13 (13.7)
one treatment-related serious emergent adverse event	n (%)	1 (1.1)	-
Patients withdrawn due to			
an emergent adverse event	n (%)	18 (19.8)	17 (17.9)
a serious emergent adverse event	n (%)	4 (4.4)	2 (2.1)
a treatment-related emergent non-serious adverse event	n (%)	12 (13.2)	14 (14.7)
a treatment-related serious emergent adverse event	n (%)	1 (1.1)	-
Patients who died	n (%)	-	-

All serious adverse events were emergent.

Emergent adverse events

In the Safety Set, the frequency of patients who reported at least one emergent adverse event during the treatment period was slightly higher in the S 12911 group (89.0%) than in the alendronate group (83.2%).

The most frequently affected system organ classes (> 10% of the patients in either group) were gastrointestinal disorders (33.0% in the S 12911 group *versus* 34.7% in the alendronate group), infections and infestations (31.9% *versus* 29.5%, respectively), musculoskeletal and connective tissue disorders (25.3% *versus* 36.8%, respectively), injury, poisoning and procedural complications (17.6% *versus* 15.8%, respectively), skin and subcutaneous tissue disorders (16.5% *versus* 18.9%, respectively), nervous system disorders (16.5% *versus* 16.8%, respectively), vascular disorders (15.4% *versus* 11.6%, respectively), eye disorders (15.4% *versus* 3.2%, respectively) and psychiatric disorders (4.4% *versus* 10.5%, respectively).

Among them, the following ones were more frequent in the S 12911 than in the alendronate group: vascular disorders (15.4% *versus* 11.6%) and eye disorders (15.4% *versus* 3.2% mainly due to cataract, see hereafter).

Conversely, musculoskeletal and connective tissue disorders as well as psychiatric disorders were less frequently reported in S 12911 group than in the alendronate group (25.3% *versus* 36.8%, and 4.4% *versus* 10.5%, respectively).

The most frequently reported emergent adverse events (> 5.0% of patients) in the S 12911 group were fall (15.4%), nasopharyngitis (13.2%), cataract (9.9%), diarrhoea (8.8%), osteoarthritis (7.7%), hypertension (6.6%), muscle spasms (6.6%), nausea (5.5%) and periodontitis (5.5%). Among these EAEs, incidences were higher in the S 12911 group than in the alendronate group for fall (15.4% versus 8.4%: the fall was reported as "accidental" by the investigator in 10 patients in the S 12911 group versus 5 in the alendronate group. None of them was considered as related to the study product by the investigator), cataract (9.9% *versus* 2.1%: 5/9 patients in the S 12911 group and 2/2 patients in the alendronate group had a medical history of cataract), diarrhoea (8.8% *versus* 4.2%) and muscle spasms (6.6% *versus* 2.1%).

On the other hand, osteoarthritis was less frequently reported in the S 12911 than in the alendronate groups (7.7% *versus* 12.6%) as well as arthralgia (none *versus* 9.5%), depression (none *versus* 5.3%) and abdominal pain upper (1.1% *versus* 5.3%).

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SAFETY RESULTS (Cont'd)

Emergent adverse events (Cont'd)

The percentage of patients having experienced at least one emergent adverse event rated as severe was higher in the S 12911 group (24.2%) than in the alendronate group (18.9%). The most frequently (> 1 patient) reported severe emergent adverse events in the S 12911 group were fall (3 patients in both groups), osteoarthritis (2 patients in both groups) and back pain (2 patients in the S 12911 group *versus* none in the alendronate group).

In the alendronate group, 2 other events were reported as severe by more than 1 patient: gastroenteritis (1 patient in the S 12911 group *versus* 3 patients in the alendronate group) and depression (none *versus* 2 patients, respectively).

Overall, 29.6% of patients had experienced at least one emergent adverse event considered to be related to the study drug by the investigator, without relevant difference between groups (29.7% *versus* 29.5% in S 12911 and alendronate groups, respectively). The most frequent in the S 12911 group were related to gastrointestinal disorders (16.5% *versus* 15.8%, respectively), skin and subcutaneous tissue disorders (7.7% *versus* 6.3%) and nervous system disorders (3.3% *versus* 4.2%) without relevant difference between groups.

Emergent adverse events led to treatment stopped in 35 patients: 18 patients (19.8%) in the S 12911 group and 17 patients (17.9%) in the alendronate group. The most frequently affected SOCs in both groups were Gastrointestinal disorders (6 patients in the S 12911 group *versus* 7 in the alendronate group) and Skin and subcutaneous tissue disorders (6 patients *versus* 4, respectively).

In most of the cases (447/582 EAEs, 76.8%), a total recovery was observed without relevant difference between groups. Overall, 121 EAEs (20.8%) did not recover with 67 EAEs (23.3%) unresolved in the S 12911 group and 54 EAEs (18.3%) in the alendronate group.

No patient died during the study. Overall, 27 patients (14.5%) experienced at least one serious emergent adverse event, without relevant difference between groups: 14 patients (15.4%) in the S 12911 group reported 15 SEAEs and 13 patients (13.7%) in the alendronate group reported 15 SEAEs. None of SEAE was reported more than once, except depression reported by 2 patients in the alendronate group. One serious emergent adverse event in the S 12911 group, iron deficiency anaemia, was considered as related to treatment according to the investigator. SEAEs led to treatment withdrawal in 4 patients in the S 12911 group for diffuse large B-cell lymphoma, iron deficiency anaemia, interstitial lung disease and breast cancer *versus* 2 patients in the alendronate group for hypertensive crisis and breast cancer.

In all, 3 SEAEs did not recover (diffuse large B-cell lymphoma and breast cancer in the S 12911 group and depression in the alendronate group).

Overall, 2 adverse events led to blind broken: one SEAE "hypertensive crisis" in the alendronate group and one non-serious EAE "dermatitis" in the S 12911 group.

Laboratory tests

As regards the biochemical parameters, the mean CPK value increased from baseline to last post-baseline in the S 12911 group (from 90.9 ± 50.0 mmol/L to 111.1 ± 63.3 mmol/L) and remained relatively stable in the alendronate group (from 86.7 ± 37.9 mmol/L to 92.0 ± 43.4 mmol/L). Consistently, the rate of patients presenting at least one emergent abnormally high CPK value was higher in the S 12911 group (14.6%) than in the alendronate group (4.9%). No patient presented emergent potentially clinically significant abnormal biochemical values for CPK (> 3ULN), creatinine or calcium.

Considering the haematological parameters, neither clinically relevant changes nor differences between groups over time were detected. The number of patients presenting at least one emergent abnormally low WBC value was lower in the S 12911 group (6.0%) than in the alendronate group (13.3%). No patient presented emergent potentially clinically significant abnormal haematological values.

Vital signs

No clinically relevant change over time or difference between groups were observed in vital signs.

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CONCLUSION

In this international, multicentre, double-blind, double-dummy, randomised study conducted in post menopausal osteoporotic women, cortical thickness at the distal tibia (14%), assessed by pQCT, increased in both S 12911 and alendronate groups after 2 years of treatment without statistically significant between-group difference.

A statistically significant between-group difference in favour of S 12911 was observed in the mean change from baseline to END for total BMD and trabecular BMD, total bone content and trabecular content at the ultradistal (4%) site of the tibia. Some bone strength parameters in the tibia were improved in the S 12911 group compared to alendronate: a statistically significant between-group difference in favour of S 12911 was observed for moment of inertia, section modulus, density weighted moment of inertia and strength strain index at the distal site (14%), for density weighted moment of inertia at less distal sites (38% and 66%) as well as strength strain index (at 66% site).

There was a slight decrease in CTX (marker of bone resorption) and increase in bone alkaline phosphatase (marker of bone formation) from baseline to END in the S 12911 group whereas both markers decreased in the alendronate group. Finally, a statistically significant increase in lumbar, total hip and femoral BMD assessed by DXA was observed in both groups with a statistically significant between-group difference in favour of S 12911 for L1-L4 lumbar and total hip.

The most frequent emergent adverse events in the S 12911 group were falls reported as accidental for most of them (slightly more frequent in the S 12911 group than in the alendronate group) and nasopharyngitis (reported in both groups without relevant difference).

Overall, safety results were in accordance with the known profile of S 12911.

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