Document title	**Clinical Study Report Synopsis**
Study title	**The efficacy and safety of a daily oral administration of S 06911 (strontium ranelate 2 g/vitamin D3 1000 IU fixed combination) on vitamin D insufficiency in the treatment of osteoporotic postmenopausal women and men.** **A prospective, international phase III study with a 6-month double-blind period to assess the efficacy and safety of a daily oral administration of S 06911 *versus* S 12911 (strontium ranelate 2 g) and a 6-month open label extension for a subgroup of patients to assess the safety of a daily oral administration of S 06911.** **Report of the M0-M12 period.**
Study drug	**S 06911 (strontium ranelate/vitamin D3)**
Studied indication	**Daily treatment of osteoporosis in men and in postmenopausal women at risk of vitamin D insufficiency.**
Development phase	**Phase III**
Protocol code	**CL3-06911-002**
Study initiation date	**26 January 2010**
Study completion date	**01 July 2011**
Main coordinator	[redacted] **Switzerland**
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 12 April 2012** **First report on M0-M6 period (NP31451)**

~~CONFIDENTIAL~~

2. SYNOPSIS

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Title of study:
The efficacy and safety of a daily oral administration of S 06911 (strontium ranelate 2 g/vitamin D_3 1000 IU fixed combination) on vitamin D insufficiency in the treatment of osteoporotic postmenopausal women and men.
A prospective, international phase III study with a 6-month double-blind period to assess the efficacy and safety of a daily oral administration of S 06911 *versus* S 12911 (strontium ranelate 2 g) and a 6-month open-label extension for a subgroup of patients to assess the safety of a daily oral administration of S 06911.
Protocol No.: CL3-06911-002
The present report describes the M0-M12 period, including the 6-month double-blind period M0-M6 and the 6-month extension period (results over M0-M6 are described in report NP31451).

International coordinator: [redacted] SWITZERLAND.
National coordinators (for countries participating in the 6-month extension period)**:** [redacted] SWITZERLAND.

Study centres:
Multicentre study: 55 active centres, 13 countries, 518 patients included.
Five countries were selected for participating in the 6-month extension period: Belgium (3 centres, 43 patients), Poland (5 centres, 103 patients), Russia (5 centres, 90 patients), Spain (6 centres, 53 patients), Switzerland (3 centres, 17 patients).

Publication: None

Studied period: Initiation date: 26 January 2010 (first selection) Last M12 visit date: 01 July 2011	**Phase of development of the study:** III

Objectives:
The primary objective was to demonstrate the efficacy of a 3-month daily oral administration of S 06911 (strontium ranelate 2 g + vitamin D_3 1000 IU), on the correction of vitamin D insufficiency (< 50 nmol/L).
The secondary objectives were:

- To demonstrate the efficacy of a 3-month daily oral administration of S 06911:
  - On the treatment of vitamin D relative insufficiency (< 75 nmol/L).
  - On the absolute change in 25-OH vitamin D
- To demonstrate the efficacy of a 6-month daily oral administration of S 06911:
  - On the correction of vitamin D insufficiency (< 50 nmol/L).
  - On the treatment of vitamin D relative insufficiency (< 75 nmol/L).
- **To evaluate the efficacy of a 12-month daily oral administration of S 06911 on the change of BMD in a subgroup of patients from selected countries.**
- **To evaluate the safety and tolerability of:**
  - A 3-month and a 6-month daily oral administration of S 06911 as compared to S 12911 (strontium ranelate 2 g).
  - **A 12-month daily oral administration of S 06911 in a subgroup of patients from selected countries.**

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Objectives (Cont'd):

- To assess the pharmacokinetics of strontium at steady state (at M3), after a repeated daily oral administration of S 06911 or S 12911.

In bold: objectives over the 12-month study period, described in the present report.

Methodology:

The study was prospective with a 6-month double-blind randomised (ratio 4:1) and parallel group period, to assess the efficacy and safety of S 06911 *versus* S 12911, and a 6-month open-label extension period, during which patients from 5 predefined countries received S 06911. The treatment allocation was stratified for country and baseline vitamin D levels.

Number of patients:

Planned: 500 patients were included at M0, with randomisation ratio 4:1 *i.e.* 400 in the S 06911 group and 100 in the S 12911 group, in order to reach at least 200 patients for the extension S 06911 period in selected countries.

Included: 518 patients were included at M0: 413 in the S 06911 group and 105 in the S 12911 group. Of these, 306 patients belonged to the 5 countries selected to participate in the 6-month extension. Finally, 257 patients were ongoing at M6 and participated in the extension period M6-M12.

Diagnosis and main criteria for inclusion

- Caucasian, men (at least 10% of the entire study population) and postmenopausal women, ≥ 50 years.
- With primary osteoporosis characterised by a Bone Mineral Density (BMD) T-score ≤ -2.5 SD at the lumbar spine or femoral neck or total hip.
- With 25-OH vitamin D serum concentration > 22.5 nmol/L (80% of patients were to have 25-OH vitamin D concentration between 22.5 nmol/L (exclusive) and 50 nmol/L (exclusive, as specified by Amendment No. 1) and 20% of patients were to have 25-OH vitamin D concentration ≥ 50 nmol/L.
- Ambulatory with BMI < 30 kg/m^2 and a satisfactory health status (life expectancy of at least one year).
- Agreeing to limit direct sunlight exposure during the first period of the study (6-month period) and to apply sunscreen (SPF ≥ 15) to exposed skin in case of exposure to direct sunlight exceeding 1 hour.

Treatments interfering with bone or calcium metabolism and treatments interfering with vitamin D absorption or catabolism were not permitted except under some conditions before or during the study. In addition, treatments interfering with strontium absorption (antiacids, tetracycline and quinolones antibiotics) were not permitted except under some conditions during the study.

Study drug over M0-M12

S 06911 (strontium ranelate 2 g / vitamin D_3 1000 IU fixed-combination), administered as one sachet per day at bedtime, preferably at least 2 hours after dinner, to be mixed with a minimum of 30 mL of water. The sachet had not to be taken with food, milk and derivate products, and medicinal products containing calcium.

Batches No's: L0031597, L0031599, L0032287, L0032982, L0033012.

Calcium supplementation 1000 mg per day was administered as 2 tablets around lunchtime.

Reference product over M0-M6 only

S 12911 (strontium ranelate 2 g), administered as one sachet per day at bedtime, preferably at least 2 hours after dinner, to be mixed with a minimum of 30 mL of water.

The sachet had not to be taken with food, milk and derivate products, and medicinal products containing calcium. Calcium supplementation 1000 mg per day was administered as 2 tablets around lunchtime.

Details on batches are provided in the study report for the M0-M6 period.

Rescue medication

One vial containing 200 000 IU of vitamin D_3 (in case of vitamin D serum level ≤ 22.5 nmol/L at M1 and/or M3).

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Duration of treatment:

- A selection period of 1 to maximum 3 weeks, extended to 4 weeks in German centres (Amendment No. 3).
- A 6-month, randomised, double-blind, 2 parallel-group period (M0-M6).
- A 6-month, open-label, one-treatment period in predefined countries (M6-M12).

Criteria for evaluation:

Efficacy measurements:

- **Serum 25-OH vitamin D concentration:** Blood samplings were carried out at selection, M1, M3, M6 and M12, on the morning of the visit, between 8 a m. and 10 a.m.
- **BMD measurement by DXA**: measurements were carried out at selection and at M12.
- **Record of falls**: the number of falls was assessed at each visit on treatment using a patient's diary. This criterion was assessed because vitamin D level has been correlated to increased muscle strength and to decreased tendency to falls in the elderly.

Safety measurements:

- **Adverse events** were collected at each visit.
- **Blood** (biochemistry including but not limited to calcemia and calciuria, haematology) **and urine parameters** (biochemistry): at selection, M3, M6 and M12.
- **Blood 1,25-$(OH)_2$ vitamin D and iPTH concentrations**: at selection, M1, M3, M6 and M12.
- **Clinical examination**: weight and height were measured at selection, M3, M6 and M12 visits and systolic and diastolic blood pressure and pulse rate at selection, inclusion, M3, M6 and M12 visits. Blood pressure and pulse rate were measured after 5 minutes rest in sitting position. A physical examination was performed at selection, M6 and M12 visits reviewing the main body systems.

Statistical methods:

Only data from patients belonging to the countries participating in the extension period were analysed.

Efficacy analysis:

Efficacy analyses were performed in the FAS extension and the PPS extension.

The FAS extension was defined as patients ongoing at M6 who had taken at least one dose of study treatment during M0-M12 and who had at least one baseline and one post baseline BMD value over M0-M12 on at least one site: Lumbar L1-L4, Femoral Neck or Total Hip.

The PPS extension was defined as all patients of the FAS extension without relevant protocol deviations that could affect the BMD evaluation.

Serum 25-OH Vitamin D

Descriptive statistics were provided for each visit and last available value over M0-M12 (End).

In case of a vitamin D rescue, 25-OH vitamin D values following a rescue dispensation were not taken into account in the efficacy analysis. These excluded values were substituted by the last value preceding the rescue.

BMD

The within S 06911 group evolution of BMD was estimated on the change from baseline to M12 and the relative change from baseline to M12, using a two-sided Student t test for paired samples. Estimate (Standard Error) of the change and the relative change from baseline, 95% confidence interval of the estimates and p-value for the t-test were provided. Descriptive statistics were also provided at baseline and at M12.

Falls

Descriptive statistics were provided over M0-M12.

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Statistical methods (Cont'd):

Safety analysis

The Safety Set extension 1 (SS1 extension) was defined as all patients from the 5 participating countries randomised to S 06911 at inclusion, and who had taken at least one dose of S 06911 over M0-M12 (S 06911/ S 06911 group).

The Safety Set extension 2 (SS2 extension) was defined as all patients from the 5 participating countries, who had taken at least one dose of S 06911 over M6-M12 (S 06911/S 06911 and S 12911/S 06911 groups).

Adverse events, laboratory parameters, vital signs were assessed through descriptive statistics over M0-M12 in the SS1 extension and over M6-M12 in the SS2 extension.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 518 patients were included in the study at M0 and randomly assigned to one of the 2 groups: 413 patients in the S 06911 group and 105 in the S 12911 group. As requested in the protocol, the randomisation was unbalanced. Of these 518 included patients, 306 patients belonged to the five selected countries participating in the 6-month extension period.

Among these 306 patients, 49 withdrew from the study before or at M6 and 257 patients did continue in the 6-month extension period (Randomised Set extension): 204 patients who had been randomised at M0 to S 06911 (S 06911/S 06911) and 53 patients to S 12911 (S 12911/ S 06911). No patient was lost to follow-up.

The disposition of patients is described in Table 1.

Table 1 - Disposition of patients

		S 06911/S 06911	S 12911/S 06911	All
Patients included at M0 in the 5 selected countries	**N**	**244**	**62**	**306**
Withdrawn before or at M6	n	40	9	49
Randomised Set extension (patients who actually participated in the extension period)	n (%)	**204**	**53**	**257**
Withdrawn over M6-M12 due to	n (%)	12 (5.9)	3 (5.7)	15 (5.8)
Adverse event	*n (%)*	*9 (2.9)*	*2 (3.8)*	*11 (4.3)*
Non-medical reason	*n (%)*	*3 (1.5)*	*1 (1.9)*	*4 (1.6)*
Completed	n (%)	**192 (94.1)**	**50 (94.3)**	**242 (94.2)**
Safety Sets				
SS1 extension	n	240	-	240
SS2 extension	n	203	53	256
Efficacy Sets				
FAS extension	n (%)	198 (97.0)	52 (98.1)	250 (97.3)
PPS extension	n (%)	175 (85.8)	49 (92.5)	224 (87.2)

% % of the Randomised Set extension

As required in the protocol, all patients in the RS extension were at least 50 years old with a range from 50 to 88 years and a mean age (± SD) of 65.6 ± 7.8 years. Most patients were women (91.4%) who were all postmenopausal (time since last menses from 2 to 43 years). The mean BMI was 25.3 ± 3.2 kg/m² with 57.2% of patients having a BMI between 25 and 30 kg/m². All patients were ambulatory; 45.1% suffered from osteoarthritis, 37.7% from hypertension, 28.4% from hypercholesterolaemia and 26.8% from spinal osteoarthritis. Consistently with medical history, the most frequent treatments at inclusion were agents acting on the renin-angiotensin system (25.7%), lipid modifying agents (24.9%), anti-inflammatory and anti-rheumatic products (21.4%), and beta-blocking agents (20.2%).

In all, 27.6% of patients had a family history of osteoporosis. 13.6% of patients had at least one previous osteoporotic vertebral fracture; 24.5% had at least one osteoporotic peripheral fracture. BMD T-score was ≤ -2.5 for 77.3% of patients at the lumbar L1-L4, 37.3% at the femoral neck and 20.8% at the total hip.

The overall mean duration of osteoporosis from diagnosis was 44.4 ± 53.5 months with a median of 21.0 months. More than half of the patients (57.6%) took previously at least one treatment for osteoporosis and/or interfering with bone metabolism.

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SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

On protocol requirement, all patients had baseline 25-OH vitamin D concentration > 22.5 nmol/L :

- 78.6% had a concentration between 22.5 (exclusive) and 50 (exclusive) nmol/L (mean = 38.7 ± 8.2 nmol/L)
- 21.4% had a concentration ≥ 50 nmol/L (mean = 65.6 ± 12.2 nmol/L).

At baseline, the mean level of 25-OH vitamin D was 44.5 ± 14.4 nmol/L.

Main baseline characteristics are summarised below in Table 2.

Table 2 - Baseline characteristics in the Randomised Set extension

		S 06911 / S 06911 (N = 204)	**S 12911 / S 06911 (N = 53)**	**All (N = 257)**
Age (years)	Mean ± SD	65.7 ± 8.0	65.5 ± 6.9	65.6 ± 7.8
	Min - Max	50 - 88	54 - 82	50 - 88
Sex	Men	19 (9.3)	3 (5.7)	22 (8.6)
	Women	185 (90.7)	50 (94.3)	235 (91.4)
BMI (kg/m^2)	Mean ± SD	25.5 ± 3.2	24.6 ± 3.2	25.3 ± 3.2
	Min - Max	16.6 - 30.6	17.8 - 29.7	16.6 – 30.6
25-OH vitamin D (nmol/L)	Mean ± SD	44.4 ± 14.6	44.9 ± 13.4	44.5 ± 14.4
	Min - Max	22.8 - 115.6	25.4 - 84.1	22.8 - 115.6
≤ 22.5	n (%)	-	-	-
]22.5 ; 50[	n (%)	161 (78.9)	41 (77.4)	202 (78.6)
≥ 50	n (%)	43 (21.1)	12 (22.6)	55 (21.4)
Lumbar L1-L4 BMD (g/cm^2)	n	203	53	256
	Mean ± SD	0.730 ± 0.076	0.716 ± 0.075	0.727 ± 0.076
	Min - Max	0.46 - 0.94	0.53 - 0.92	0.46 - 0.94
T-score ≤ -2.5	n (%)	153 (75.4)	45 (84.9)	198 (77.3)
Femoral neck BMD (g/cm^2)	n	203	52	255
	Mean ± SD	0.612 ± 0.083	0.585 ± 0.066	0.606 ± 0.081
	Min - Max	0.37 - 0.84	0.41 - 0.74	0.37 - 0.84
T-score ≤ -2.5	n (%)	70 (34.5)	25 (48.1)	95 (37.3)
Total Hip BMD (g/cm^2)	n	203	52	255
	Mean ± SD	0.739 ± 0.110	0.706 ± 0.096	0.733 ± 0.108
	Min ; Max	0.34 - 0.97	0.49 - 0.91	0.34 - 0.97
T-score ≤ -2.5	n (%)	36 (17.7)	17 (32.7)	53 (20.8)

No relevant differences in baseline characteristics were observed in patients randomised to S 06911 or S 12911 at inclusion in the population participating in the extension study. In addition, this population had similar baseline characteristics as the overall population included in the study at M0.

The global treatment compliance to S 06911 or S 12911 over M0-M6 and to S 06911 over M6-M12 was satisfactory (*i.e.* between 80% and 120%) in 91% of the patients overall over M0-M12. The overall mean global compliance over M0-M12 was 92.8 ± 10.2%.

Six patients from the RS extension had a vitamin D rescue at M1 and/or M3 visits (one patient in the S 06911/ S 06911 group and five in the S 12911/S 06911 group).

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS

25-OH vitamin D serum concentration

Details on the 25-OH vitamin D analysis over M0-M6 are provided in the main study report (NP31451).

Description of 25-OH vitamin D concentration over M0-M12 in the FAS extension

In the group of patients randomised to S 06911 at inclusion (S 06911/S 06911, N = 198), the mean concentration of 25-OH vitamin D increased from baseline (44.3 ± 13.8 nmol/L) to M1 (57.8 ± 14.1 nmol/L) and to M3 (64.3 ± 14.6 nmol/L) with no further increase at M6 (68.1 ± 16.6 nmol/L) and M12 (60.8 ± 13.9 nmol/L). The proportion of patients having a level ≥ 50 nmol/L increased from 21.2% at baseline to 81.1% at M12.

In the group of patients randomised to S 12911 at inclusion (S 12911/ S 06911, N = 52), the mean concentration of 25-OH vitamin D roughly remained stable from baseline (45.2 ± 13.4 nmol/L) to M6, *i.e.* while on S 12911 treatment, and then increased as expected from M6 to M12 (57.5 ± 17.2 nmol/L) *i.e.* while on S 06911 treatment. The proportion of patients having a level ≥ 50 nmol/L increased from 23.1% at baseline to 75% at M12.

The efficacy of a daily oral administration of S 06911 on the correction of vitamin D described over the M0-M6 period in the corresponding study report was here confirmed over the M0-M12 period.

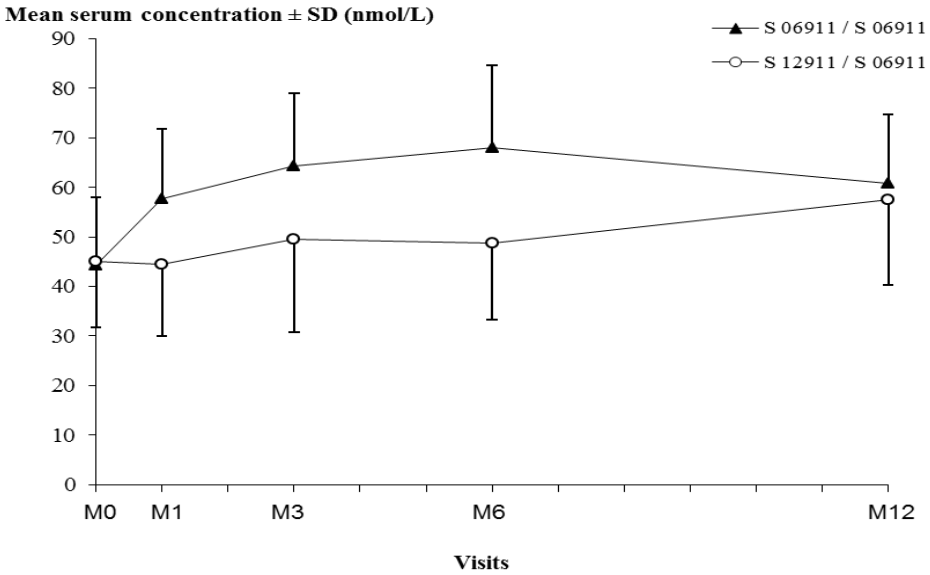
Figure 1 shows the profile of 25-OH vitamin D mean concentration over M0-M12 in patients randomised to S 06911 or S12911 at inclusion (S 06911/ S 06911 or S 12911/ S 06911, respectively) in the FAS extension.

The slight increase observed from M1 to M3 in patients treated with S 12911 was probably related to sunlight exposure, since M3 visits were generally performed during summer (for 91.0% of the patients from June to September).

In the FAS extension, the proportion of patients having a level ≥ 50 nmol/L was 86.4%, 89.9% and 81.1% at M3, M6 and M12 respectively in the S 06911/S 06911 group and 44.2%, 48.1% and 75.0% respectively in the S 12911/S 06911 group.

In the PPS extension, results were similar to those observed in the FAS extension.

Figure 1 - 25-OH vitamin D mean serum concentration (nmol/L) at each visit over M0-M12 in the FAS extension



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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY (Cont'd)

Evolution of BMD in the S 06911/S 06911 group (FAS extension) over M0-M12 (Table 3)

Mean **lumbar L1-L4** BMD: relative change from baseline to M12 was +5.51 ± 5.83 %. The increase over time was statistically significant (E (SE) = 5.5 (0.4) %, 95% CI = [4.7 ; 6.3], p < 0.001).

Mean **femoral neck** BMD: relative change from baseline to M12 was +4.05 ± 5.38 %. The increase over time was statistically significant (E (SE) = 4.1 (0.4) %, 95% CI = [3.3 ; 4.8], p < 0.001).

Mean **total hip** BMD: relative change from baseline to M12 was +3.38 ± 4.42 %. The increase over time was statistically significant (E (SE) = 3.4 (0.3) %, 95% CI = [2.8 ; 4.0], p < 0.001).

Similar results were observed in the PPS extension.

The BMD annual mean relative changes in patients from the S 12911/S 06911 group were of the same order of magnitude as in patients from the S 06911/S 06911 group, suggesting that the duration of vitamin D intake had no major influence on the mean BMD evolution during the study.

In addition, the annual BMD relative change results were consistent with those observed previously in the SOTI study (NP08338) over the first year of treatment with S 12911, with an annual increase of +5.9 ± 7.4 % for lumbar L1-L4 BMD, +2.0 ± 4.5 % for femoral neck, + 3.2 ± 4.7 % for total hip.

Table 3 - Lumbar L1-L4, femoral neck and total hip BMD absolute (g/cm²) and relative (%) changes from baseline to M12 in the FAS extension

		S 06911 /S 06911 (N = 198)		
BMD (g/cm²)		**L1-L4 Lumbar**	**Femoral neck**	**Total Hip**
Baseline	Mean ± SD	0.728 ± 0.075	0.613 ± 0.084	0.743 ± 0.106
	Min - Max	0.46 - 0.94	0.37 - 0.84	0.43 - 0.97
M12	Mean ± SD	0.768 ± 0.083	0.637 ± 0.084	0.768 ± 0.109
	Min ; Max	0.50 ; 1.02	0.44 ; 0.89	0.45 ; 1.01
Relative change from baseline to M12 (%)				
	Mean ± SD	5.51 ± 5.83	4.05 ± 5.38	3.38 ± 4.42
	Min ; Max	-15.2 ; 27.1	-5.6 ; 30.4	-10.4 ; 20.3
	E (SE)[(1)]	5.51 (0.41)	4.05 (0.38)	3.38 (0.31)
	95%CI[(2)]	[4.70 ; 6.33]	[3.30 ; 4.81]	[2.76 ; 4.00]
	p value[(3)]	***< 0.001***	***< 0.001***	***< 0.001***
Change from baseline to M12 (g/cm²)				
	Mean ± SD	0.039 ± 0.042	0.024 ± 0.030	0.024 ± 0.031
	Min ; Max	-0.12 ; 0.20	-0.04 ; 0.14	-0.07 ; 0.14
	E (SE)[(1)]	0.039 (0.003)	0.024 (0.002)	0.024 (0.002)
	95%CI[(2)]	[0.033 ; 0.045]	[0.019 ; 0.028]	[0.020 ; 0.029]
	p value[(3)]	***< 0.001***	***< 0.001***	***< 0.001***

n number of patients assessable; (1) Estimate (Standard error) of the difference between means at baseline and M12; (2) 95% Confidence Interval of the estimate; (3) two-sided Student's t test for paired sample

Incidence of falls

In the FAS extension, the proportion of patients who experienced at least one post-baseline fall over M0-M12 was 30% in the S 06911/S 06911 group and 39% in the S 12911/S 06911 group.

Similar results were observed in the PPS extension.

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS

Over M0-M12 in the SS1 extension, the overall frequency of patients who reported at least one **emergent adverse event** was 81.7%.

The most frequently affected system organ classes were injury, poisoning and procedural complications (30.8%), infections and infestations (27.9%), musculoskeletal and connective tissue disorders (25.0%), gastrointestinal disorders (23.8%) and nervous system disorders (17.5%).

The most commonly reported emergent adverse events were falls (25.8%), diarrhoea (6.3%), nasopharyngitis (6.3%), back pain (5.8%), arthralgia (5.4%), headache (5.0%), hypertension (4.6%) and bronchitis (4.2%). The high incidence of falls was due to a specific event tracking for efficacy assessment. Blood creatine phosphokinase increased was reported in 4.2% of patients (events of mild or moderate intensity).

No specific emergent adverse events potentially related to vitamin D intake, such as hypercalcaemia, proteinuria, nephrolithiasis or nephrocalcinosis, were reported. Hypercalciuria was reported in 8 patients (3.3%) and urine calcium increased in 4 patients (1.7%). All cases were asymptomatic. Hypercalciuria was considered related to S 06911 by the investigator in 4 patients. None of the cases were severe or serious, or led to treatment withdrawal.

The emergent adverse events observed with strontium ranelate combined to vitamin D_3 (S 06911) were in accordance with those expected with strontium ranelate (S 12911) and no unexpected events arose from S 12911 combined to vitamin D_3.

Safety results obtained over M0-M12 on the SS1 extension (N = 240) are summarised in Table 4.

Table 4 - Overall summary of safety results in the SS1 extension over M0-M12

		S 06911 / S 06911 (N = 240)
Patients having reported		
at least one emergent adverse event	n (%)	196 (81.7)
at least one treatment-related emergent adverse event	n (%)	49 (20.4)
Patients having experienced		
at least one serious emergent adverse event	n (%)	21 (8.8)
at least one treatment-related serious emergent adverse event	n (%)	-
Patients withdrawn from treatment		
due to an adverse event	n (%)	34 (14.2)
Patients who died	n (%)	-

In the SS1 extension, most emergent adverse events were graded as mild or moderate (95.8% of the events).

Severe emergent adverse events occurred in 28 patients (4.1%). The system organ classes most commonly affected were gastrointestinal disorders (1.7%) and nervous system disorders (1.5%). Two severe emergent adverse events (oral hypoasthesia and headache) were considered related to S 06911 by the investigator.

Treatment-related emergent adverse events were reported in 49 patients (20.4%). The system organ classes most commonly affected were gastrointestinal disorders (8.3%), skin subcutaneous disorders (3.8%), musculoskeletal and connective tissue disorders (3.3%).

Premature discontinuation of treatment due to adverse events affected 34 patients (14.2%). Events responsible for treatment withdrawal concerned mainly gastrointestinal disorders (5.0%), skin and subcutaneous disorders, musculoskeletal and connective tissue disorders (2.9% each). Preferred terms reported more than once were nausea, headache and arthralgia (3 cases), diarrhoea, dyspepsia, pruritus, bone pain (2 cases each).

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Name of Finished Product: **Not available**	**Volume:**	
Name of Active Ingredient: **Strontium ranelate/vitamin D_3** **S 06911**	**Page:**	

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Con'd)

Emergent serious adverse event were reported in 21 patients (8.8%). The most frequently affected system organ class was nervous system disorders (2.1%). The preferred terms reported more than once were transient ischaemic attack (3 cases) and cataract operation (2 cases). None was considered treatment-related.
No case of deep vein thrombosis was reported during the 12-month treatment with S 06911.
No death was reported in patients on S 06911 during the 12-month study period.

A total of 78 patients (32.5%) were identified with **biochemical** emergent potentially clinically significant abnormal (PCSA) values. Most PCSA values concerned changes in phosphocalcic homeostasis parameter: decrease in blood calcium (21.8%) and increase in blood phosphorus (9.6%). These changes were expected according to the mechanism of action of strontium ranelate and were observed in previous studies.
High values of urinary calcium/creatinine ratio were observed in 29 patients (12.9%). No high PCSA value was observed (considering the upper PCSA limit defined in SOTI and TROPOS studies, *i.e.* > 3.36).
As regards abnormalities potentially associated with vitamin D intake, hypercalciuria was reported as adverse events in 8 patients with 4 events considered as treatment-related by the investigator and, urinary calcium increased was reported as adverse events in 4 patients with one event considered as treatment-related by the investigator. Note that hypercalciurias were diagnosed from a spot urine test, usually not considered as accurate as a 24h-urine sampling to diagnose a clinically relevant hypercalciuria.
High blood calcium values were reported in 11 patients (4.9%). These values were PCSA in 3 patients. For two of these 3 patients, the values returned within the normal range on S 06911 treatment at the subsequent visit. In the third patient, the PCSA value reported at M12 (2.65 mmol/l) was close to the baseline value (2.63 nmol/L, alert value: 2.64 nmol/L).
All cases were asymptomatic (no symptom events of vitamin D toxicity such as high calcemia or renal lithiasis were reported). None were severe or serious, or led to treatment withdrawal.

A total of 22 patients (9.2%) were identified with iPTH emergent low PCSA values.
Two patients had levels of vitamin D ≥ 125 nmol/L, one at M6 and the other at M12. For the patient with a level of vitamin D ≥ 125 nmol/L at M6, the concentration spontaneously decreased on S 06911 treatment 6 months later at M12. For the patient with a level of vitamin D ≥ 125 nmol/L at M12, it was noted a vitamin D level of 98.5 nmol/L at baseline, 122.8 nmol/L at M3 and 107.8 nmol/L at M6. No safety concern was raised in both patients with high value of vitamin D.

No clinically relevant changes over the 12-month treatment with S 06911 were detected for **haematology parameters**.
No clinically relevant changes were detected for **vital signs.**

The SS2 consisted of 203 patients from the S 06911/S 06911 group, all included in the SS1 extension and therefore described above, and 53 patients from the S 12911/S 06911 group, for whom safety results over M6-M12 were as follows: out of these 53 patients, 2 reported 3 SAE: ischaemic stroke and loss of consciousness in the same patient and hypertension in another patient. The ischaemic stroke led to study treatment withdrawal. No other EAEs were responsible for treatment withdrawal in this group of patients. Two events were considered related to the study drug and were both related to gastrointestinal disorders (diarrhoea and dry mouth). No VTE was observed. No death was reported. In addition, no specific adverse events potentially related to vitamin D toxicity (such as hypercalcemia, nephrolithiasis) were reported.
In all, no unexpected safety results were observed in the SS2 extension over M6-M12.

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CONCLUSION

The efficacy of S 06911 (fixed association of strontium ranelate 2 g and vitamin D_3 1000 IU) on the correction of vitamin D insufficiency demonstrated over the M0-M6 period in osteoporotic postmenopausal women and men aged ≥ 50 years, was confirmed in the subset of patients participating in the extension period (up to M12).

On S 06911 treatment over M0-M12, the percentage of patients with a corrected 25-OH vitamin D level (≥ 50 nmol/L) increased from 21.2% at baseline to 86.4% at M3 and was maintained up to M12 (81.1%).

In addition, BMD significantly increased at all assessed sites in patients treated with S 06911 during one year (+5% in L1-L4 Lumbar BMD, +4% in femoral neck BMD and +3% in total hip BMD), consistently with annual BMD changes reported with S 12911 in previous studies.

The safety profile of S 06911 was similar to that of strontium ranelate, with no unexpected events arising from its combination to vitamin D_3.

Date of the report: 12 April 2012