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 deficiency in the treatment of osteoporotic postmenopausal women and men. A 12-month prospective, open labelled, one treatment group international phase III study.**
Study drug	**S 06911 (strontium ranelate 2g/ vitamin D3 1000 IU fixed combination)**
Studied indication	**Daily treatment of osteoporosis in men and in postmenopausal women at risk of vitamin D insufficiency**
Development phase	**Phase III**
Protocol code	**CL3-06911-003**
Study initiation date	**02 March 2010**
Study completion date	**22 June 2011**
Main coordinator	[redacted] **- Switzerland**
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France** **LABORATORIOS SERVIER, S.L.** **Departamiento de Investigación y Desarrollo** **Avenida de los Madroños, 33** **parque del Conde de Orgaz** **28043 Madrid - Spain**
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 10 April 2012**

~~CONFIDENTIAL~~

2. SYNOPSIS

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Title of study:
The efficacy and safety of a daily oral administration of S 06911 (strontium ranelate 2g/vitamin D3 1000 IU fixed combination) on vitamin D deficiency in the treatment of osteoporotic postmenopausal women and men.
A 12-month prospective, open labelled, one treatment group international phase III study.
Protocol No.: CL3-06911-003

International coordinator: [redacted] SWITZERLAND.
National coordinators: [redacted], SWITZERLAND.

Study centres:
Multicentric study (12 active centres, 6 countries, 19 patients included).
Belgium (1 centre, 2 patients), Poland (4 centres, 5 patients), Russia (2 centres, 3 patients), Slovakia (2 centres, 4 patients), Spain (2 centres, 3 patients), Switzerland (1 centre, 2 patients).

Publication : Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 2 March 2010 (*first selection)* Completion date: 22 June 2011 (*last completed visit*)	III

Objectives:
Primary objective:

- To evaluate the efficacy of a 12-month daily oral administration of S 06911 (strontium ranelate 2 g + vitamin D_3 1000 IU) on the correction of vitamin D insufficiency (*i.e.* to increase the serum 25-OH vitamin D level to a value ≥ 50 nmol/L) in patients with a baseline deficient vitamin D level (*i.e.* ≤ 22.5 nmol/L).

Secondary objectives:

- To evaluate the efficacy of a 12-month daily oral administration of S 06911 on the absolute change in serum 25-OH-vitamin D.
- To evaluate the efficacy of a 12-month daily oral administration of S 06911 on the correction of vitamin D deficiency (*i.e.* to increase 25-OH vitamin D to a value > 22.5 nmol/L).
- To evaluate the safety and tolerability of a 12-month daily oral administration of S 06911.

Methodology:
The study was a 12-month open-label one-treatment-group prospective, international, phase III study, in osteoporotic men and post-menopausal women with a deficient serum 25-OH vitamin D level (*i.e.* ≤ 22.5 nmol/L). The recruitment was done in parallel to the recruitment in the pivotal CL3-06911-002 study conducted in patients with vitamin D insufficiency.

Number of patients:
Planned: 60 patients
Included: 19 patients (due to difficulties in recruitment in this study performed in parallel to CL3-06911-002)

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Diagnosis and main criteria for inclusion:

- Caucasian, men (at least 10% of the entire study population) or 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.
- Ambulatory with BMI < 30 kg/m^2 and a satisfactory health status (life expectancy of at least one year to be able to participate to the entire course of the study).

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:
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: L0031110, L0032984.
Calcium supplementation 1000 mg per day was administered as 2 tablets around lunchtime.
Batch No. L0031483.

Rescue medication:
One vial containing 200000 IU of vitamin D_3 (in case vitamin D serum level ≤ 22.5 nmol/L at M3 and/or M6).

Duration of treatment:

- A selection period of 1 to maximum 3 weeks.
- A 12-month, open-label, one-treatment-group period.

Criteria for evaluation:
Efficacy measurements:

- Primary criterion: **serum 25-OH vitamin D concentration** over M0-M12 period

Blood samplings were carried out at selection, M3, M6 and M12 visits, between 8 a.m. and 10 a m.

- Secondary criteria:

Ensuring an appropriate vitamin D level has been correlated to a decrease tendency to falls (Holick, 2007) and an increase in muscle strength of older people (Boonen, 2006):

- **Record of falls**: the number of falls was assessed using a patient's diary, to be recorded on the paper CRF at each patient's visit starting at inclusion.
- **Physical performance**: the Short Physical Performance Battery (SPPB) was performed at inclusion, M6 and M12. The three components of this battery were balance tests, gait speed test and chair-stand test. The SPPB score ranges from 0 to 12, 0 to 4 for each component (a higher score indicates an improvement).

Safety measurements:

- **Adverse events** were collected at each visit.
- **Blood (including transaminases and CPK) and urine parameters (including calcium, phosphorus and creatinine)**: samples were collected at selection, M3, M6 and M12 visits.
- **1,25 $(OH)_2$ vitamin D and PTH concentrations**: blood samples were collected at selection, M3, M6 and M12 visits.
- **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. A physical examination was performed at selection, M6 and M12 visits reviewing the main body systems.

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Statistical methods:

Efficacy analysis:

Based on the intention-to-treat principle, the FAS was defined as all included patients who had taken at least one dose of study treatment and who had at least one post-baseline (M3 or M6 or M12) value of serum 25-OH vitamin D.

Primary criterion: serum 25-OH Vitamin D

- The proportion of patients with level of **25-OH vitamin D ≥ 50 nmol/L** at End (last post-baseline available value) was described with its 95% Exact Clopper-Pearson confidence interval (CI) based on a binomial distribution. The same analysis was performed at M3, M6 and M12.
- The evolution of 25-OH vitamin D was estimated on the **change from baseline** to each visit and to End using a parametric approach (95% CI based on a Student t test for paired samples) and a non-parametric approach (95% CI based on Walsh averages).
- The proportion of patients with level of **25-OH vitamin D > 22.5 nmol/L** was described at each visit and End with its 95% Exact Clopper-Pearson CI based on a binomial distribution.

Secondary criteria:

Falls: Descriptive statistics.

Short Physical Performance Battery (SPPB): The evolution of SPPB Total Score (and each 3 sub-scores) was estimated on the change from baseline to each visit and to End using a parametric approach (95% CI based on a Student t test for paired samples) and a non-parametric approach (95% CI based on Walsh averages).

Safety analysis:

The safety analysis was performed on the Safety Set.

Adverse events, laboratory parameters, vital signs were assessed through descriptive statistics.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Due to difficulties in recruitment, only 19 patients were selected and included instead of the 60 patients planned. Out of them, 3 patients were withdrawn: 1 due to adverse event (perioral dermatitis) and two on their own decision. Finally, 16 patients completed the study at M12.

Table 1 - Disposition of patients by group

	All
Included	**19**
Lost to follow-up	**-**
Withdrawn due to	**3**
adverse event	1
non-medical reason	2
Completed	**16**
Included Set (IS)	**19**
Full Analysis Set (FAS)	**18**
Safety Set	**19**

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SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Main baseline characteristics are summarised below in Table 2:

Table 2 - Baseline characteristics in the Included Set

		S 06911 (N = 19)
Age	Mean ± SD	65.5 ± 8.5
	Min - Max	54 - 84
Sex	Women	18
	Men	1
BMI (kg/m^2)	Mean ± SD	25.9 ± 2.8
	Min - Max	19.6 - 29.7
Lumbar L1-L4 BMD (g/cm^2)	Mean ± SD	0.745 ± 0.122
	Min - Max	0.48 - 1.14
25-OH vitamin D (nmol/L)	Mean ± SD	18.8 ± 1.9
	Min - Max	15.4 - 22.4
SPPB Total score	Mean ± SD	9.1 ± 1.8
	Min - Max	6 - 12

As required in the protocol, all patients were at least 50 years old with a range from 54 to 84 years. 18 out of the 19 included patients were women who were all postmenopausal (time since last menses from 2 to 34 years). All patients were ambulatory. Current smoking habits were reported by 37% of the patients. 52.6% of patients suffered from hypertension, 31.6% from osteoarthritis, 21.1% from spinal osteoarthritis and 21.1% from varicose vein. The most frequent treatments at inclusion were agents acting on the renin-angiotensin system (47.4%), anti-inflammatory and anti-rheumatic products (36.8%), beta-blocking agents (21.1%), calcium channel blockers (15.8%) and psycholeptics (15.8%).

In all, 21.1% of patients had a family history of osteoporosis; 15.8% of patients had at least one previous osteoporotic vertebral fracture and 21.1% had at least one previous osteoporotic peripheral fracture. As required, BMD T-score was ≤ -2.5 SD at lumbar spine or femoral neck or total hip.

The overall mean duration of osteoporosis from diagnosis was 40.2 ± 42.4 months with a median of 20 months. About 42% of patients took previously at least one treatment for osteoporosis and/or interfering with bone metabolism.

Most patients had a good functioning of lower extremity assessed by the SPPB at baseline with a mean total score of 9.1 ± 1.8 (normal range between 10 and 12 points).

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

Study treatment compliance during M0-M12 period was satisfactory (*i.e.* between 80% and 120%) in 78.9% of the patients. The mean compliance was of 84.7 ± 15.8%.

A similar mean compliance was observed for calcium (80.2 ± 19.2%).

No patient required a vitamin D rescue.

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS

- **Primary assessment criterion: 25-OH vitamin D serum concentration**

Main analysis: ***Proportion of patients with 25-OH vitamin D level ≥ 50 nmol/L at End***.

In the FAS, the proportion of patients with a 25-OH vitamin D level ≥ 50 nmol/L at End over the M0-M12 period was of 66.7% (95% CI [41 ; 87]%).

The correction in 25-OH vitamin D deficiency (end value > 22.5 nmol/L) was achieved in all patients but one, who had stopped the study treatment more than 3 weeks before sampling.

Secondary analysis

Change from baseline to End over M0-M12 period

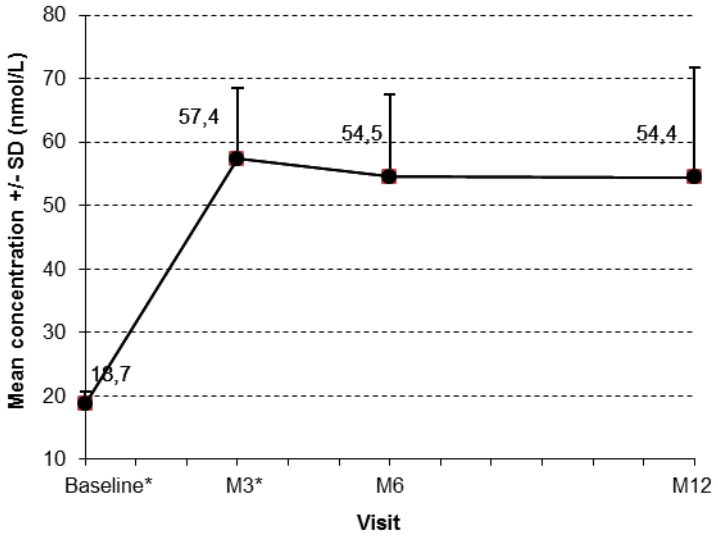
The mean increase in 25-OH vitamin D serum level from baseline to End was 35.7 ± 16.7 nmol/L.

Evolution of 25-OH vitamin D concentration during the study

The mean serum level of 25-OH vitamin D increased from baseline (18.7 ± 1.9 nmol/L) to M3 (57.4 ± 11.1 nmol/L) and remained stable at M6 (54.5 ± 13.1 nmol/L) and at M12 (54.4 ± 17.3 nmol/L).

In the FAS, 77.8%, 68.8% and 68.8% patients had a serum 25-OH vitamin D ≥ 50 nmol/L at M3, M6 and M12, respectively.

Figure 1 - 25-OH vitamin D- Mean concentration during the M0-M12 period- FAS



*18 patients at baseline and M3, 16 patients at M6 and M12

- **Secondary assessment criteria**

Out of the 18 assessed patients over M0-M12, 7 patients experienced at least one fall.

There was a trend to an improvement in SPPB total score from baseline to last post-baseline value over M0-M12 with a non-statistically significant mean increase of +0.3 ± 1.7 (95% CI [-0.14 ; 0.64]%) and a median increase of 1.0.

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS

The Safety Set consisted of the 19 included patients.

Table 3 - Overall summary of safety results

		S 06911 (N = 19)
Patients having reported		
at least one emergent adverse event	n (%)	15 (78.9)
at least one treatment-related emergent adverse event	n (%)	2 (10.5)
Patients having experienced		
at least one serious emergent adverse event	n (%)	1 (5.3)
at least one treatment-related serious emergent adverse event	n (%)	-
Patients withdrawn from treatment		
due to an adverse event	n (%)	1 (5.3)
Due to a treatment-related adverse event	n (%)	-
Patients who died	n (%)	-

The **most frequently affected system organ classes** were injury, poisoning and procedural complications (7 patients out of the 19), gastrointestinal disorders, infections and infestations (4 patients each), musculoskeletal and connective tissue disorders, ear and labyrinth disorders (3 patients each).

The **most commonly reported emergent adverse events** were fall (5 patients- 2 patients with a fall reported in efficacy were not reported as EAE because for one was not emergent and the other was induced by a car accident), vertigo (3 patients), back pain, joint sprain and hypercalciuria (2 patients each). The high incidence of falls could be explained by a specific event tracking during the trial. Most observed emergent adverse events were expected events in the osteoporotic population and in accordance with the known safety profile of strontium ranelate.

All emergent adverse events were graded as mild or moderate, except one vertigo, graded as severe. The event was considered as not related to the study drug by the investigator.

Two events were reported as treatment-related: one vertigo and one diarrhoea of mild and moderate intensity, respectively.

One patient prematurely discontinued the study due to a perioral dermatitis (of mild intensity), considered as not related to the study drug by the investigator.

One serious adverse event was reported: a pubis fracture after the patient being hit by a car when cycling. The event was considered as not related to S 06911 treatment.

Neither Venous Thromboembolic Events (VTE) nor Central Nervous System (CNS) events were reported during the study.

No Death occurred during the study.

Laboratory safety tests

No clinically relevant changes over time were detected for **biochemistry and haematology parameters.**

Changes observed in phosphocalcic homeostasis parameters (*i.e*. a decrease in blood calcium and an increase in blood phosphorus) were expected according to the mechanism of action of strontium ranelate.

Two patients presented a high urinary calcium/creatinine ratio. 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, two cases of hypercalciuria were reported as adverse events of mild intensity. 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. No symptoms were associated with any of these biochemical abnormalities.

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Regarding the **endocrinological** parameters, as could be expected, there was an increase in mean 1,25 $(OH)_2$ vitamin D levels and a decrease in mean PTH levels.

No clinically relevant changes over time were detected for **vital signs.**

CONCLUSION

This 12-month open-label study investigated 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 in osteoporotic patients with deficiency in serum vitamin D (≤ 22.5 nmol/L), aged ≥ 50 years.

It was planned to include 60 patients in parallel to the recruitment of the pivotal CL3-06911-002 study, but due to difficulties in recruitment, the study was conducted in 19 patients.

Two thirds of patients reached a serum 25-OH vitamin D level ≥ 50 nmol/L at their last post-baseline evaluation and all of them except one (who was no more on treatment at the time of the sampling) had serum 25-OH vitamin D level > 22.5 nmol/L. No patient required a vitamin D rescue.

The mean serum 25-OH vitamin D level increased from 18.7 ± 1.9 nmol/L at baseline to 57.4 ± 11.1 nmol/L at M3 and then remained stable up to M12 (54.4 ± 17.3 nmol/L).

The safety profile of S 06911 was in accordance with the known safety profile of strontium ranelate, with no unexpected events arising from its combination to vitamin D_3.

Date of the report: 10 April 2012.