

Document title **Clinical Study Report**

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-labelled extension for a subgroup of patients to assess the safety of a daily oral administration of S 06911.
Report of the M0-M6 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 **14 January 2011**

Main coordinator **[REDACTED]
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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 11 April 2012**

CONFIDENTIAL

2. SYNOPSIS

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<p>Title of study: 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 <i>versus</i> S 12911 (strontium ranelate 2 g) and a 6-month open-labelled extension for a subgroup of patients to assess the safety of a daily oral administration of S 06911. Protocol No.: CL3-06911-002</p> <p>The present report describes the M0-M6 period. 12-month results will be described in a separate report (NP31521).</p> <p>International coordinator: ██████████ ██████████ SWITZERLAND.</p> <p>National coordinators: ██████████ AUSTRIA, ██████████ BELGIUM, ██████████ CZECH REPUBLIC, ██████████ FINLAND, ██████████ FRANCE, ██████████ GERMANY, ██████████ HUNGARY, ██████████ POLAND, ██████████ RUSSIA, ██████████ SLOVAKIA, ██████████ SPAIN, ██████████ SWITZERLAND and ██████████ UK.</p> <p>Study centres: Multicentre study (55 active centres, 13 countries, 518 patients included). Austria (3 centres, 4 patients), Belgium (3 centres, 43 patients), Czech Republic (3 centres, 32 patients), Finland (3 centres, 8 patients), France (5 centres, 25 patients), Germany (7 centres, 25 patients), Hungary (4 centres, 76 patients), Poland (5 centres, 103 patients), Russian federation (5 centres, 90 patients), Slovakia (4 centres, 19 patients), Spain (6 centres, 53 patients), Switzerland (3 centres, 17 patients), United Kingdom (4 centres, 23 patients).</p> <p>Publication: ██████████. <i>Osteoporos. Int.</i> (2012) 23: (Suppl 2): S85-S386.</p>		
<p>Studied period: Initiation date: 26 January 2010 (first selection) Last M6 visit date: 14 January 2011</p>		<p>Phase of development of the study: III</p>

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<p>Objectives: The primary objective was to demonstrate the efficacy of a 3-month daily oral administration of S 06911 (strontium ranelate 2 g + vitamin D₃ 1000 IU), on the correction of vitamin D insufficiency (< 50 nmol/L). The secondary objectives were:</p> <ul style="list-style-type: none"> - To demonstrate the efficacy of a 3-month daily oral administration of S 06911: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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 in selected countries*. - To evaluate the safety and tolerability of: <ul style="list-style-type: none"> • 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 in selected countries*. - To assess the pharmacokinetics of strontium at steady state, after a repeated daily oral administration of S 06911 or S 12911 (PK report). <p>* 12-month results will be described in a separate report.</p>		
<p>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 <i>versus</i> S 12911 and a 6-month open-label extension period for a subgroup of patients to assess the safety of S 06911, in osteoporotic men and post-menopausal women. The treatment allocation was stratified for country and baseline vitamin D levels.</p>		
<p>Number of patients: Planned: 500 patients with randomisation ratio 4:1 <i>i.e.</i> 400 in the S 06911 group and 100 in the S 12911 group (in order to reach 200 patients for the extension S 06911 open-label treatment period in selected countries). Included: 518 patients: 413 in the S 06911 group and 105 in the S 12911 group. 306 patients belonged to the 5 countries participating in the open-label period.</p>		
<p>Diagnosis and main criteria for inclusion:</p> <ul style="list-style-type: none"> - 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/m² and a satisfactory health status (life expectancy of at least one year to be able to participate in the entire course of the study). - 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. <p>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.</p>		

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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. Calcium supplementation 1000 mg per day was administered as 2 tablets around lunchtime. <u>Batches No's:</u> L0031597, L0031599, L0032287, L0032982.		
Reference product: 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. <u>Batches No.'s:</u> L0031601, L0032289, L0032299		
Rescue medication: One vial containing 200000 IU of vitamin D ₃ (in case of vitamin D serum level \leq 22.5 nmol/L at M1 and/or M3).		
Duration of treatment: <ul style="list-style-type: none"> - 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. - A 6-month, open-label, one-treatment period (subgroup of at least 200 patients in predefined countries). 		
Criteria for evaluation: <u>Efficacy measurements:</u> <ul style="list-style-type: none"> - Primary criterion: serum 25-OH vitamin D concentration over M0-M3 period Blood samplings were carried out at Selection, M1, M3, M6 and M12 visits, between 8 a.m. and 10 a.m. The main analytical approach was the proportion of patients with a 25-OH vitamin D concentration \geq 50 nmol/L at End, <i>i.e.</i> last available value between 1 and 3 months of treatment (before any vitamin D rescue). Secondary analyses were done using a similar approach at M3 and M6, on the proportion of patients with a 25-OH vitamin D concentration \geq 75 nmol/L at End, M3 and M6 and on serum 25-OH vitamin D expressed in terms of absolute and relative changes from baseline to End, M3 and M6. - Secondary criteria: <ul style="list-style-type: none"> • Record of falls: the number of falls was assessed using a patient's diary, to be recorded on the e-CRF at each patient's visit starting at inclusion. • Physical performance: the Short Physical Performane Battery (SPPB) was performed at inclusion, M3 and M6. The three components of this battery were balance tests, gait speed test and chairstand test. • BMD measurement by DXA: BMD measurements by DXA were carried out at selection in all patients and at M12 in the subgroup of patients participating in the second period of the study. This efficacy criterion will be presented in the second report which will take into account the additional 6-month-treatment period. 		

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<p>Criteria for evaluation (Cont'd):</p> <p><u>Safety measurements:</u></p> <ul style="list-style-type: none"> - Adverse events were collected at each visit. - Blood biochemistry (including but not limited to calcemia and calciuria, haematology: blood samples were collected at selection, M3, M6 and M12 visits. - Urine biochemistry: urine 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, M1, 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. 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. <p><u>Pharmacokinetic measurements:</u></p> <p>Three blood samples at M3 and one blood sample the day after M3 were collected for pharmacokinetic analysis in a subgroup of at least 200 patients.</p>		
<p>Statistical methods:</p> <p><u>Efficacy analysis:</u></p> <p>The FAS was defined as all randomised patients who had taken at least one dose of study treatment and who had at least one post baseline value of 25-OH vitamin D over the M0-M3 period. The SubFAS was defined as all patients of the FAS with a baseline 25-OH vitamin D serum concentration < 50 nmol/L (<i>i.e.</i> patients with baseline vitamin D deficiency). The PPS was defined as all patients of the FAS without relevant protocol deviations that could affect the effect of the study drug on the primary criterion.</p> <p><i>In case of a vitamin D rescue, 25-OH vit D values following a rescue dispensation were not taken into account in the efficacy analysis. These excluded values were substituted by the last recorded value preceding the rescue.</i></p> <p>Primary criterion: serum 25-OH vitamin D</p> <p><u>Main analysis</u></p> <p>Treatment groups were compared in the FAS on the proportion of patients with levels of 25-OH vitamin D ≥ 50 nmol/L at End (<i>i.e.</i> last post-baseline value over M0-M3), using a logistic regression model including treatment, country and classes of baseline vitamin D levels as factor ($22.5 ; 50$; ≥ 50 nmol/L). The following elements were provided: Estimates (Standard Error) (E(SE)) of the odds-ratio between groups, 95% confidence interval (CI), and the associated p-value.</p> <p>The same analysis was conducted in the Sub-FAS (but without adjusting on classes of baseline vitamin D levels) and the PPS.</p> <p>The treatment effect on the proportion of patients with levels of 25-OH vitamin D ≥ 50 nmol/L at End (over M0-M3 period) was estimated in the FAS, in the SubFAS and in the PPS using a logistic regression model without adjustment, including only treatment effect:</p> <ul style="list-style-type: none"> - E (SE) of the odds-ratio between groups was provided with its 95% CI, as well as the corresponding p-value. - E (SE) of the difference between group of percentages of patients with 25-OH vitamin D ≥ 50 nmol/L was provided with its 95% CI. 		

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<p>Statistical methods (Cont'd): <u>Secondary analysis</u> Similar analyses were done at M3 and M6 visits. Treatment groups were also compared on absolute and relative changes in 25-OH vitamin D from Baseline to End, M3 or M6 (using a general linear model studying adjusted treatment effect), and on the proportion of patients with levels of 25-OH vitamin D ≥ 75 nmol/L at End, M3 and M6 (using logistic regression model studying adjusted treatment effect). Unadjusted analyses using the logistic regression model were performed on the proportion of patients with vitamin D ≥ 75 nmol/L (without adjustment, including only treatment effect).</p> <p>Secondary criteria: Falls and Short Physical Performance Battery (SPPB) Falls <u>Adjusted analysis</u> Treatment groups were compared in the FAS and in the PPS, on the proportion of patients experiencing at least one post-baseline fall, using a logistic regression model including treatment, country, classes of baseline vitamin D levels ($22.5 ; 50[; \geq 50$ nmol/L) and baseline value of fall (Yes/No) as factors. E (SE) of the odds-ratio between groups and 95% CI were provided. <u>Unadjusted analysis</u> The treatment effect on the proportion of patients experiencing at least one post-baseline fall was estimated in the FAS and in the PPS using a logistic regression model without adjustment, including only treatment effect: Estimate (Standard Error) of the odds-ratio between groups was provided with its 95% CI. E (SE) of the difference between group percentages for occurrence of falls was provided with its 95% CI.</p> <p>Short Physical Performance Battery (SPPB) Treatment groups were compared on the relative change in SPPB score and sub-scores from baseline to M3 and to M6, using a general linear model studying treatment effect, with country and classes of baseline vitamin D levels ($22.5 ; 50[; \geq 50$ nmol/L) as covariates (fixed effect), in the FAS and the PPS. Estimates of the difference, Standard error of the estimates, 95% CI were provided. The same analysis was performed on the changes from baseline to M3 and M6 adjusting on score at baseline (continuous data) in addition to country and classes of baseline vitamin D levels. Treatment groups were also compared on the proportion of patients having a score ≥ 10 at M3 and at M6, using a logistic regression model including treatment, country, classes of baseline vitamin D levels ($22.5 ; 50[; \geq 50$ nmol/L) and SPPB Total score at baseline in classes ($< 10 ; \geq 10$) as factors in the FAS and the PPS.</p> <p>Safety analysis: Adverse events, laboratory parameters, vital signs were assessed through descriptive statistics.</p> <p>Pharmacokinetics analysis: The pharmacokinetics of strontium at steady state, following repeated oral administration of S 06911 or S 12911 was analyzed using a population pharmacokinetic approach and secondary pharmacokinetic parameters (AUC and C_{max}) were computed. This analysis is the object of a separate report.</p>		

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SUMMARY - CONCLUSIONS**STUDY POPULATION AND OUTCOME**

A total of 518 patients were included in this study 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 distribution was unbalanced. The disposition of patients is described in Table 1.

Table 1 - Disposition of patients by group

		S 06911	S 12911	All
Included - Randomised Set (RS)	N	413	105	518
Lost to Follow-up	n (%)	-	-	-
Withdrawn from the study due to	n (%)	67 (16.2)	13 (12.4)	80 (15.4)
adverse event	n (%)	38 (9.2)	7 (6.7)	45 (8.7)
non-medical reason	n (%)	25 (6.1)	5 (4.8)	30 (5.8)
protocol deviation	n (%)	4 (1.0)	1 (1.0)	5 (1.0)
Completed at M6	n (%)	346 (83.8)	92 (87.6)	438 (84.6)
Full Analysis Set (FAS)	n (%)	394 (95.4)	104 (99.0)	498 (96.1)
SUB-Full Analysis Set (SUB-FAS)	n (%)	315 (76.3)	85 (81.0)	400 (77.2)
Per Protocol Set (PPS)	n (%)	336 (81.4)	89 (84.8)	425 (82.0)
Safety Set	n	407	105	512

% (n/N)*100

Main baseline characteristics are summarised below in Table 2:

Table 2 - Baseline characteristics in the Randomised Set

		S 06911 (N = 413)	S 12911 (N = 105)	All (N = 518)	
Age (years)	Mean ± SD	66.9 ± 8.3	66.6 ± 8.0	66.8 ± 8.3	
	Min ; Max	50 ; 89	54 ; 86	50 ; 89	
Sex	Men	41 (9.9)	8 (7.6)	49 (9.5)	
	Women	372 (90.1)	97 (92.4)	469 (90.5)	
BMI (kg/m²)	Mean ± SD	25.3 ± 3.3	25.0 ± 3.0	25.3 ± 3.2	
	Min ; Max	15.3 ; 32.5	17.8 ; 29.9	15.3 ; 32.5	
	< 20	n (%)	31 (7.5)	5 (4.8)	36 (7.0)
	[20 - 25[n (%)	147 (35.6)	46 (43.8)	193 (37.3)
	[25 - 30[n (%)	229 (55.5)	54 (51.4)	283 (54.6)
	>= 30	n (%)	6 (1.5)	-	6 (1.2)
Lumbar L1-L4 BMD	n	408	103	511	
	Mean ± SD	0.736 ± 0.094	0.743 ± 0.105	0.738 ± 0.096	
	Min ; Max	0.455 ; 1.310	0.526 ; 1.209	0.455 ; 1.310	
T-score ≤ -2.5	n (%)	301 (73.8)	80 (77.7)	381 (74.6)	
25-OH vitamin D (nmol/L)	Mean ± SD	44.0 ± 14.9	44.4 ± 13.3	44.1 ± 14.6	
	Min ; Max	22.6 ; 115.6	25.4 ; 84.1	22.6 ; 115.6	
	≤ 22.5	n (%)	-	-	-
]22.5 ; 50[n (%)	333 (80.6)	85 (81.0)	418 (80.7)
	≥ 50	n (%)	80 (19.4)	20 (19.1)	100 (19.3)
SPPB Total score	Mean ± SD	9.9 ± 1.8	9.7 ± 2.1	9.9 ± 1.9	
	Min ; Max	4 ; 12	1 ; 12	1 ; 12	

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<p>SUMMARY - CONCLUSIONS (Cont'd)</p> <p><u>STUDY POPULATION AND OUTCOME (Cont'd)</u></p> <p>As required in the protocol, all patients were at least 50 years old with a range from 50 to 89 years. Most were women (90.5%) who were all postmenopausal (time since last menses from 2 to 49 years). 9.9% of the patients were men in the S 06911 group and 7.6% in the S 12911. All patients were ambulatory. Current smoking habits were reported by 15% of patients in the S 06911 group and 10.5% in the S 12911 group. 41.5% of patients suffered from hypertension, 31.1% from osteoarthritis, 24.1% from hypercholesterolaemia and 20.1% from spinal osteoarthritis. The most frequent treatments at inclusion were agents acting on the renin-angiotensin system (27.6%), beta-blocking agents (22.6%), lipid modifying agents (22.4%) and anti-inflammatory and anti-rheumatic products (18.0%).</p> <p>In all, 24.6% of patients had a family history of osteoporosis; 10.6% of patients had at least one previous osteoporotic vertebral fracture and 21.8% had at least one previous osteoporotic peripheral fracture. BMD T-score was ≤ -2.5 for 74.6% of patients at the lumbar L1-L4, 14.6% at the left total hip, 17.1% at the right total hip, 35.5% at the left femoral neck and 29.2% at the right femoral neck.</p> <p>The overall mean duration of osteoporosis from diagnosis was 41.8 ± 54.5 months with a median of 14.5 months. More than half of patients (53.7%) took previously at least one treatment for osteoporosis and/or interfering with bone metabolism.</p> <p>Most patients had a good functioning of lower extremity assessed by the SPPB score at baseline, 62.3% of patients having a mean total score between 10 and 12 with a mean total score of 9.9 ± 1.9.</p> <p>On protocol requirement, all patients had baseline 25-OH vitamin D concentration > 22.5 nmol/L :</p> <ul style="list-style-type: none"> - 80.7% had a concentration between 22.5 (exclusive) and 50 (exclusive) nmol/L (mean = 38.5 ± 7.8 nmol/L) and - 19.3% had a concentration ≥ 50 nmol/L (mean = 67.7 ± 12.7 nmol/L). <p>At baseline, the mean level of 25-OH vitamin D was 44.1 ± 14.6 nmol/L.</p> <p>Study treatment compliance during M0-M6 period was very close in average in both treatment groups: $88.9 \pm 20.2\%$ in the S 06911 group and $91.8 \pm 16.0\%$ in the S 12911 group and was satisfactory (<i>i.e.</i> between 80% and 120%) in 83.5% of the patients.</p> <p>Ten patients had a vitamin D rescue at M1 and/or M3 visits (3 patients in the S 06911 group and 7 in the S 12911 group).</p> <p><u>Pharmacokinetic analysis results</u></p> <p>The pharmacokinetic population for S 12911 included 67 patients (5 men and 62 women) and for S 06911, 245 patients (30 men and 215 women).</p> <p>The pharmacokinetic of strontium after repeated oral administrations of strontium ranelate in combination with vitamin D₃ (S 06911) was similar to the PK of strontium observed after repeated administrations of strontium ranelate alone (S 12911).</p>		

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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 ≥ 50 nmol/L at End (i.e. last post-baseline value over M0-M3).

In the FAS, the proportion of patients with a 25-OH vitamin D level ≥ 50 nmol/L at End over M0-M3 period (Table 3) was higher in the S 06911 group (83.8%) than in the S 12911 group (44.2%). Using a logistic regression model adjusted for country and baseline vitamin D levels (main analysis), the odds ratio (OR) was estimated at 6.7 (95% CI [4.2 ; 10.9] and was highly statistically significant ($p < 0.001$). The unadjusted analysis between groups difference was 39.5% with an unadjusted OR of 6.5 (95% CI [4.1 ; 10.4], $p < 0.001$), consistent with the 30% targeted in the protocol.

Table 3 - Distribution of patients according to their 25-OH vitamin D serum level at End over M0-M3 period - FAS

25-OH vitamin D concentration		S 06911 (N = 394)	S 12911 (N = 104)
≥ 50 nmol/L	n (%)	330 (83.8)	46 (44.2)
< 50 nmol/L	n (%)	64 (16.2)	58 (55.8)

Main analysis:

Logistic regression model	E (SE)	(1.1)	6.7 (1.6)
	95% CI	(2)	[4.2 ; 10.9]
	p-value	(3.1)	< 0.001

Unadjusted analysis

Logistic regression model	E (SE)	(1.2)	6.5 (1.6)
	95% CI	(2)	[4.1 ; 10.4]
	p-value	(3.2)	< 0.001

Difference between percentages

	E (SE)	(1.3)	39.5 (5.2)
	95% CI	(2)	[29.3 ; 49.7]

% (n/N)*100; (1.1) E(SE) of the adjusted odds ratio (OR) between groups for 25-OH vit D ≥ 50 nmol/L S 06911 / S 12911; (2) 95% confidence interval (CI) of the estimate; (3.1) difference test between S06911 and S12911, logistic regression model with country and baseline vitamin D levels as factor ratio likelihood test; (1.2) E(SE) of the unadjusted OR between groups for 25-OH vit D ≥ 50 nmol/L S 06911 / S 12911; (3.2) difference test between S06911 and S12911, chi-square test ratio likelihood test (corresponding to logistic regression in this analysis); (1.3) E(SE) of the difference between groups percentages for 25-OH vit D ≥ 50 nmol/L S 06911 - S 12911

Note For 3 patients in the S 06911 group and 7 patients in the S 12911 group who required a vitamin D rescue, the 25-OH vitamin D values reported after the rescue were substituted with the last value preceding the rescue.

Similar results were observed in the Sub-FAS and the PPS:

- In the Sub-FAS (set of patients with a baseline vitamin D insufficiency), the correction of the insufficiency was achieved at End (over M0-M3 period) for 82.2% of patients in the S 06911 group *versus* 38.8% in the S 12911 group (adjusted OR = 7.4, 95%CI [4.4 ; 12.5], $p < 0.001$).
- In the PPS (set of patients without relevant protocol deviations), the correction of the insufficiency was achieved at End (over M0-M3 period) for 85.1% of patients in the S 06911 group *versus* 43.8% in the S 12911 group (adjusted OR = 7.8, 95%CI [4.6 ; 13.3], $p < 0.001$).

Results in the FAS, Sub-FAS and PPS using the logistic regression model without adjustment were similar to those observed with the main analysis.

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SUMMARY - CONCLUSIONS (Cont'd)EFFICACY RESULTS (Cont'd)Secondary analyses in the FAS:**Proportion of patients with 25-OH vitamin D \geq 50 nmol/L at M3 and at M6**

The proportion of patients having a 25-OH vitamin D level \geq 50 nmol/L was significantly higher ($p < 0.001$) in the S 06911 group than in the S 12911 group at M3 (84.4% *versus* 44.9%, estimated adjusted OR of 6.8 [4.2 ; 11.2]) as well as at M6 (86.0% *versus* 40.0%, estimated adjusted OR of 12.7 [7.1 ; 22.7]).

Change/Relative change in 25-OH vitamin D concentration from baseline to End over M0-M3 period

In the S 06911 group, the 25-OH vitamin D concentration increased from 44.2 ± 15.2 nmol/L at baseline to 64.8 ± 16.6 nmol/L at End, corresponding to an increase of 20.6 ± 18.8 nmol/L.

In the S12911 group, the 25-OH vitamin D concentration increased from 44.1 ± 13.0 nmol/L at baseline to 49.1 ± 18.7 nmol/L at End, corresponding to an increase of 5.0 ± 18.8 nmol/L.

The estimated adjusted mean difference between groups of 15.7 nmol/L (95% CI [12.1 ; 19.2]) was statistically significant in favour of S 06911 ($p < 0.001$).

Relative changes were 59.0 ± 58.4 % in the S 06911 group *versus* 15.6 ± 47.5 % in the S 12911 group, corresponding to a statistically significant between-group difference of 43.3% (95% CI [31.2 ; 55.5], $p < 0.001$).

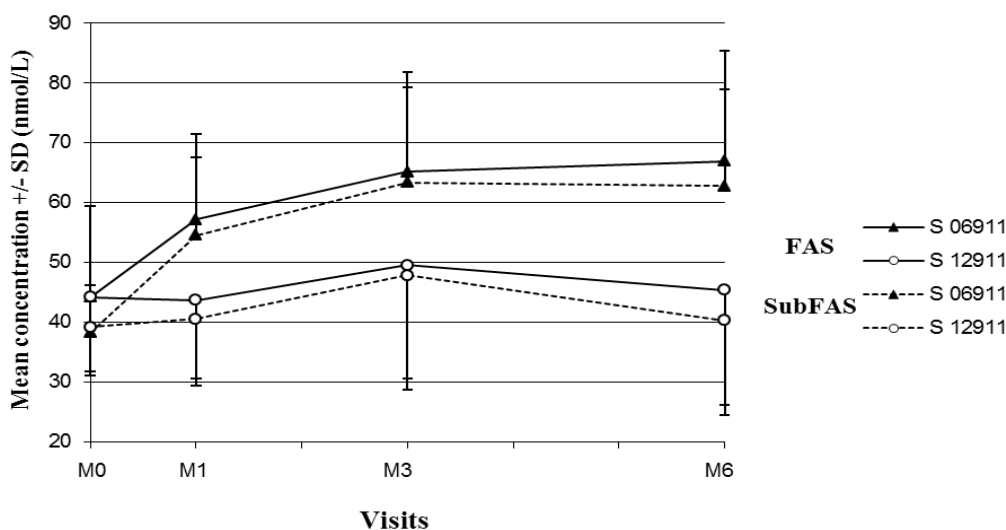
Proportion of patients with 25-OH vitamin D \geq 75 nmol/L at End over M0-M3 period

The proportion of patients with a level \geq 75 nmol/L at End was significantly higher in the S 06911 group (23.9%) than in the S 12911 group (7.7%), the estimated adjusted OR being of 4.0 (95%CI [1.8 ; 8.6]; $p < 0.001$).

Description of 25-OH vitamin D concentration during the study

Figure 1 shows the profile of 25-OH vitamin D mean concentration during the study in the FAS and the Sub-FAS. The observed fluctuations were probably caused by direct sunlight exposure: M3 visits were mainly performed during summer, for 91% of the patients from June to September.

Figure 1 - 25-OH vitamin D mean concentration (nmol/L) during the study in the FAS and the Sub-FAS



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SUMMARY - CONCLUSIONS (Cont'd)EFFICACY RESULTS (Cont'd)**Secondary assessment criteria**

The secondary efficacy criteria were the proportion of patients who experienced at least one post-baseline fall and the SPPB score.

In the FAS over M0-M6, 16.5% of patients in the S 06911 group and 20.2% of patients in the S 12911 group experienced at least one post-baseline fall.

The SPPB score improved in both treatment groups from baseline to M3 and to M6 in the FAS. The relative changes in SPPB score from baseline to M6 were of $3.9 \pm 16.9\%$ in the S 06911 group and $4.5 \pm 16.4\%$ in the S 12911 group.

No statistically significant between-group differences were observed on these secondary criteria.

SAFETY RESULTS

The Safety Set consisted of 512 patients: 407 patients in the S 06911 group and 105 in the S 12911 group. Safety results are summarised in Table 4.

Table 4 - Overall summary of safety results

		S 06911 (N = 407)	S 12911 (N = 105)
Patients having reported			
at least one emergent adverse event	n (%)	275 (67.6)	73 (69.5)
at least one treatment-related emergent adverse event	n (%)	59 (14.5)	16 (15.2)
Patients having experienced			
at least one serious emergent adverse event (including 1 death)	n (%)	21 (5.2)	9 (8.6)
at least one treatment-related serious emergent adverse event	n (%)	-	1 (1.0)
Patients withdrawn from treatment			
due to an adverse event	n (%)	39 (9.6)	7 (6.7)
Patients who died	n (%)	1 (0.2)	-

The overall frequency of patients who reported at least one emergent adverse event was very close in the S 06911 and S 12911 groups (67.6% and 69.5%, respectively).

The most frequently affected system organ classes were gastrointestinal disorders (18.2% in the S 06911 group and 21.9% in the S 12911 group), injury, poisoning and procedural complications (17.2% and 22.9%, respectively), musculoskeletal and connective tissue disorders (16.2% and 21.0%, respectively). Most system organ classes were reported at comparable incidence in both groups, except investigations (mainly events related to laboratory values), less frequently reported in the S 06911 group (6.9%) than in the S 12911 group (14.3%).

Emergent adverse events were similarly reported in patients with a baseline vitamin D ≥ 50 nmol/L or < 50 nmol/L in the S 06911 group over the 6-month study period.

In the S 06911 group, the most commonly reported emergent adverse events were fall (14.0% in the S 06911 group and 20.0% in the S 12911 group), hypercalciuria (6.9% and 2.9%, respectively), diarrhoea (4.7% and 6.7%, respectively). Falls were reported with a high incidence in both S 06911 or S 12911 groups due to a specific event tracking for efficacy assessment. No relevant between-group differences were observed.

The incidences of emergent adverse events were in both groups in accordance with those expected with S 12911.

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SAFETY RESULTS (Cont'd)		
<p>Most emergent adverse events were graded as mild or moderate (about 95.0% of the events in both treatment groups). Severe emergent adverse events occurred with a similar frequency in both groups: in 27 patients (6.6%) in the S 06911 group and 7 patients (6.7%) in the S 12911 group.</p> <p>One severe emergent adverse event in the S 06911 group (oral hypoesthesia) and 2 in the S 12911 group (diarrhoea and lacunar infarction) were considered as related to the study treatment by the investigator.</p> <p>Treatment-related emergent adverse events were reported in 75 patients: 59 patients (14.5%) in the S 06911 group and 16 patients (15.2%) in the S 12911 group. The system organ classes most commonly affected were gastrointestinal disorders in both treatment groups (6.9% of the patients in the S 06911 group and 7.6% in the S 12911 group), skin subcutaneous disorders (2.7% and 1.0%, respectively) and musculoskeletal and connective tissue disorders (1.7% and 1.9%, respectively).</p> <p>Premature discontinuation of treatment due to adverse events affected 39 patients (9.6%) in the S 06911 group and 7 patients (6.7%) in the S 12911 group. Events responsible for treatment withdrawal concerned mainly gastrointestinal disorders (2.9% and 1.0%, respectively) and skin and subcutaneous disorders (2.0% and 1.0%, respectively). Preferred terms reported more than once were diarrhoea (4 cases), dyspepsia (3 cases), and nausea, pruritus, rash erythematous, arthralgia, bone pain, oedema peripheral, headache (2 cases each) in the S 06911 group, and none in the S 12911 group.</p> <p>Emergent serious adverse events were reported in 30 patients: 21 patients (5.2%) in the S 06911 group and 9 patients (8.6%) in the S 12911 group. The most frequently affected system organ classes were nervous system disorders (1.2% of the patients in the S 06911 group and 1.0% in the S 12911 group) and cardiac disorders (1.0% of the patients in both treatment groups). The only preferred term reported more than once was transient ischaemic attack (4 cases in the S 06911 group). Two serious adverse events (lacunar infarction and loss of consciousness) observed in one patient of the S 12911 group were considered treatment-related. No case of deep vein thrombosis was reported over the 6-month study period.</p> <p>Death occurred in one male patient of the S 06911 group from congestive heart failure. The patient aged 78 years had a history of coronary heart disease with heart failure and was on related appropriate therapies. The death was considered as not related to the study treatment according to the investigator.</p> <p>Laboratory safety tests</p> <p>Neither clinically relevant changes over time nor differences between groups were detected for biochemistry and haematology parameters.</p> <p>Changes observed in phosphocalcic homeostasis parameters (<i>i.e.</i> a decrease in blood calcium and an increase in blood phosphorus) were expected according to the mechanism of action of strontium ranelate. One patient with increased CPK (reported as PCSA value) was withdrawn from the study. The CPK value returned to normal range after treatment discontinuation.</p> <p>High values of urinary calcium/creatinine ratio were reported in 44 patients (11.6%) of the S 06911 group and in 9 patients (9.0%) of the S 12911 group. One high PCSA value was observed in a patient of the S 06911 group (considering the Upper PCSA limit defined in SOTI and TROPOS studies, <i>i.e.</i> > 3.36).</p> <p>As regards abnormalities potentially associated, hypercalciuria was reported as adverse event in 28.7% of the patients in the S 06911 group and 22.0% in the S 12911 group. 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 PCSA values were reported in 3 patients (0.8%) and 1 patient (1.0%), respectively, none of the cases being reported as adverse events. No particular symptoms such as renal lithiasis or nephrocalcinosis were associated with these abnormalities.</p> <p>Regarding the endocrinological parameters, the increase in mean 1,25-(OH)₂ vitamin D was higher in the S 06911 group than in the S 12911 group.</p>		

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<p>A similar profile in clinical laboratory results was observed in patients from the S 06911 group with a baseline vitamin D ≥ 50 nmol/L or < 50 nmol/L over the 6-month study period, except for 1,25-(OH)₂ vitamin D: no change was observed after 6 months of treatment in patients with a baseline vitamin D ≥ 50 nmol/L while an increase was observed in patients with a baseline vitamin D < 50 nmol/L.</p> <p>Five patients had levels of vitamin D ≥ 125 nmol/L at M3 (1 patient) or at M6 (4 patients). They were all on S 06911 treatment. For the patient with a level of vitamin D ≥ 125 nmol/L at M3, the concentration spontaneously decreased on S 06911 treatment 3 months later at M6. No safety concern was raised in these patients with high value of vitamin D.</p> <p>No clinically relevant changes over time or between-group differences were detected for vital signs.</p>		
CONCLUSION		
<p>This randomised double-blind study demonstrated the efficacy of S 06911 (fixed association of strontium ranelate 2 g and vitamin D₃ 1000 IU) over S 12911 (strontium ranelate 2 g alone) on the correction of vitamin D insufficiency in osteoporotic men and postmenopausal women, aged ≥ 50 years.</p> <p>The percentage of patients with a 25-OH vitamin D serum level ≥ 50 nmol/L at the last evaluation over the first 3 months of treatment (main efficacy criterion) was significantly higher in the S 06911 group (83.8%) than in the S 12911 group (44.2%) (Odds Ratio = 6.7, $p < 0.001$). The between-group difference in the percentages of patients with 25-OH vitamin D level over the threshold value of 50 nmol/L after 3 months of treatment (39.5%) was consistent with the 30% targeted in the protocol. In the population of patients with a baseline level of 25-OH vitamin D < 50 nmol/L, who represented 80.3% of the overall population, the between-group difference reached 43.4%.</p> <p>The safety profile of S 06911 was similar to that of strontium ranelate, with no unexpected events arising from its combination to vitamin D₃.</p>		
Date of the report: 11 April 2012		