2. SYNOPSIS

Name of Company: I.R.I.S. 6 place des Pleiades 92415 Courbevoie - FRANCE	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study: SOTI and TROPOS Phase III Studies Open-labelled EXTENSION.
The long term efficacy and long term safety assessment of a three-year oral administration of S 12911 in osteoporotic postmenopausal women having participated either to Spinal Osteoporosis Therapeutic Intervention "SOTI" study or to TReatment Of Peripheral OSteoporosis "TROPOS" study.
A three-year multicentric multinational open study with S 12911.
Protocol No.: CL3-12911-012

Coordinators: [redacted]

Study centres: Multicentre study with 63 active centres in 11 countries, 2055 patients included:
Australia (6 centres, 130 patients included), Belgium (5 centres, 269 patients included), Denmark (4 centres, 73 patients included), France (12 centres, 222 patients included), Germany (6 centres, 99 patients included), Hungary (3 centres, 114 patients included), Italy (12 centres, 349 patients included), Poland (4 centres, 468 patients included), Spain (6 centres, 203 patients included), Switzerland (1 centre, 4 patients included), United Kingdom (4 centres, 124 patients included).

Publication (reference): Not applicable.

Studied period:	**Phase of development:**
Initiation date: 09 September 2002. Completion date: 17 February 2007.	III

Objectives:
- To assess the efficacy of an additional 3-year oral administration of strontium ranelate SR (and calcium/vitamin D supplementation) on bone mineral density (BMD), on the number of patients experiencing new osteoporotic fractures, on body height and on bone markers in the SOTI and TROPOS patients having already received strontium ranelate for 4 or 5 years (*i.e.* more than 4 years).
- To allow patients treated with placebo in the main part of the SOTI study or for 5 years in the TROPOS study to receive active treatment for a duration known to be effective on vertebral fracture.
- To assess the safety of an additional 3-year oral administration of SR (and calcium/vitamin D supplements) in SOTI and TROPOS patients having already received strontium ranelate for 4 or 5 years.
- To assess the safety of a 3-year oral administration of SR (and calcium/vitamin D supplements) in patients treated with placebo in the main part of the SOTI or TROPOS studies.

Methodology: Open, international, multicentre study.
- Run-in period (F.I.R.S.T. study (NP 08582 report)) designed to start the normalisation of calcium and/or vitamin D patient's status, with individually adapted calcium and/or vitamin D supplementation (duration from 2 weeks to 6 months).
- Patients were to be included either in SOTI or TROPOS studies (double-blind placebo controlled studies with 2 parallel groups, one assigned to SR and one to placebo):
  - SOTI: treatment period of 3 years (NP 08338: M0-M36 report) extended to 4 years (NP 22819: M0-M48 report) and 5 years (NP 22821: M48-M60 report).
  - TROPOS: treatment period of 3 years (NP 08340: M0-M36 report) extended to 5 years (NP 22824: M0-M60 report).
- **3-year open extension study (present report), all patients were to receive SR.**

Number of patients:
- Planned: 3600 patients (all patients were to be treated with strontium ranelate).
- Included: 2055 patients.

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Diagnosis and main criteria for inclusion:

Caucasian postmenopausal osteoporotic women, having participated in the SOTI or TROPOS studies up to the M60 visit either under study treatment (placebo or SR), or having interrupted the study treatment within the 6-month period preceding the M60 visit.

Patients having had their SOTI-TROPOS M60 or withdrawal visit within 1-year preceding the protocol set-up in the centre could be included in the study CL3-12911-012.

Study treatment: Strontium ranelate sachets of yellowish fine granules for oral suspension containing 2 g of active principle. The daily dose was 2 g of active principle (1 sachet/day, in the evening at bedtime).

- Batch No.'s: K05566, K05567, K05568, K05569, K05570, K06515, K06516, K06517, K06518, K06633, K06634, K06635, K06636, K07684, K07685, K07686, K07687, K07688, K10538, K10539, K10540, K10541, K11615, K11616, K11617, K11618, K07687, L00005, L00007, L00029, L00038, L00040, L02568, L02569, L02570, L02571, L05509, L05511, L05513, L05514, L07503, L07504, L07505, L07506.

All patients received calcium and vitamin D supplementation individually adapted (calcium: 0, 500 or 1000 mg/day and vitamin D: 500 to 1000 IU/day during 5 days per week in Poland or 400 to 800 IU/day in other countries, taken at lunchtime).

Reference product: Not applicable.

Duration of treatment:

- 5-year follow-up in the previous SOTI or TROPOS studies with SR or placebo (M0-M60).
- **3-year treatment open period in the extension study (inclusion in the extension study-M96), which is the object of the present report.**

Criteria for evaluation:

Efficacy measurements:

- BMD of lumbar spine, femoral neck, and total hip, assessed by DXA at inclusion in the extension study and every 12 months (M72, M84, and M96).
- Occurrence of new vertebral fractures assessed by spinal radiographs at inclusion and every 12 months in patients having had spinal radiographs in SOTI or TROPOS. Centralised readings of each X-ray were performed according to the semi-quantitative method of Genant (0 – III grading for T4 to L4 vertebrae, L5 being assessed as fractured or not). A new vertebral fracture was defined as a grade ≥ I vertebral deformity occurring in a previously normal (non-deformed) vertebra.
- Occurrence of new peripheral fractures assessed at inclusion, and every 6 months (M66, M72, M78, M84, M90 and M96).
- Body height, initially planned in the study protocol as efficacy criterion was analysed as safety criterion.
- Biochemical markers of bone metabolism initially planned in the study protocol were not finally assessed.

Safety measurements:

- Adverse events reported at each visit.
- Laboratory safety tests assessed at inclusion, and every 12 months. Biochemistry: albumin, blood and urinary creatinine, total alkaline phosphatases, ASAT, ALAT, Gamma-GT (GGT), bilirubin, creatine kinase (CK) total and CK isoenzymes (in case of abnormal high CK value), blood calcium, and haematology; hemostasis parameters in patients in case of venous thromboembolic event.
- Vital signs assessed every 6 months for weight, BMI, sitting systolic and diastolic blood pressures, heart rate, and every 12 months for body height.
- Iliac bone biopsy was proposed to patients previously treated with SR in SOTI or TROPOS studies. Biopsies were to be performed in the M72-M96 period with an additional evaluation 6 months and 12 months after SR treatment discontinuation.
- Falls of the patients and circumstances related to these falls were recorded at each visit.

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Criteria for evaluation (Cont'd)

Drug concentrations:

- Serum strontium concentration was quantified by high frequency inductively coupled plasma emission spectrophotometry (ICP) at inclusion, and every 6 months during the study. In Denmark, additional measurements were performed 3 and 6 months after stopping SR treatment. However, these results will be presented in a separate report.
- Bone strontium and calcium content at the iliac level was measured by ICP in the M72-M96 period, and 6 months or 12 months after SR treatment discontinuation (for patients having performed biopsies). These results will be presented in a separate report.

Statistical methods:

Efficacy analyses:

The Full Analysis Set (FAS) was defined as all patients of the Included Set having taken at least one sachet of the study drug after inclusion in the extension study, having at least one baseline and one post baseline assessable lumbar BMD or at least one evaluation of fracture (vertebral or peripheral) after inclusion in the extension study.

Five treatment groups were defined according to the treatment groups the patients belonged to during M0-M60 in either SOTI or TROPOS studies as follows:

- SR treatment during the whole M0-M60 period, one group having participated in SOTI (**SOTI SR** group No. 1) and one in TROPOS (**TROPOS SR** group No. 4).
- SR treatment during M0-M48 period and placebo during the M48-M60 period (**SOTI SR/Placebo** group No. 2)
- Placebo during the whole M0-M60 period (**TROPOS Placebo** group No. 5).
- Placebo during M0-M48 period and SR during the M48-M60 period (**SOTI Placebo/SR** group No. 3).

BMD of lumbar spine, femoral neck, and total hip were mainly expressed as:

- Change and relative change from the visit of the first SR intake in SOTI or TROPOS to each visit and to the last available value on treatment in the extension study.
- Change and relative change from inclusion in the extension study to each visit and to the last available value on treatment in the extension study.

Descriptive analyses were provided by treatment groups and pooling patients treated with SR for the whole 8-year follow-up period.

Occurrence of new fractures (vertebral and/or peripheral) were mainly expressed as:

- Cumulative incidence from the first SR intake of patients with at least one new fracture by the Kaplan Meïer method, using one year as the interval of interest, and presented for each group.
- Incidence at each year with the corresponding 95% confidence interval presented for each group.

These two analyses were also performed pooling patients treated with SR for the whole 8-year follow-up period.

Safety analysis:

Descriptive statistics from the first SR intake in SOTI or TROPOS or from inclusion in the extension study were provided in the Safety Set for: adverse events including venous thromboembolic events (VTE) and neurological disorders, blood and urinary biochemistry, creatine kinase (CK) total and CK isoenzymes, sum of blood calcium and strontium, haematology, vital signs (weight, height, BMI, and blood pressure). In addition, descriptive statistics were provided for falls occurring from inclusion in the extension study.

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SUMMARY – CONCLUSIONS

STUDY POPULATION AND OUTCOME

Overall patients disposition

Status		**SOTI SR (N = 154)**	**SOTI SR/Placebo (N = 164)**	**SOTI Placebo/SR (N = 300)**	**TROPOS SR (N = 739)**	**TROPOS Placebo (N = 698)**	**ALL (N = 2055)**
Total duration of SR treatment		8 years	7 years	4 years	8 years	3 years	
Included	**n**	**154**	**164**	**300**	**739**	**698**	**2055**
In compliance with the protocol	n (%)	129 (83.8)	144 (87.8)	245 (81.7)	655 (88.6)	610 (87.4)	**1783 (86.8)**
With a PD at inclusion in the extension study	n (%)	25 (16.2)	20 (12.2)	55 (18.3)	84 (11.4)	88 (12.6)	**272 (13.2)**
Lost to follow-up	**n (%)**	**1 (0.6)**	**1 (0.6)**	**1 (0.3)**	**14 (1.9)**	**8 (1.1)**	**25 (1.2)**
Withdrawn due to	**n (%)**	**28 (18.2)**	**32 (19.5)**	**70 (23.3)**	**248 (33.6)**	**232 (33.2)**	**610 (29.7)**
Non-medical reason	n (%)	16 (10.4)	20 (12.2)	39 (13.0)	139 (18.8)	129 (18.5)	**343 (16.7)**
Adverse event	n (%)	8 (5.2)	11 (6.7)	27 (9.0)	96 (13.0)	93 (13.3)	**235 (11.4)**
Osteoporosis aggravated	n (%)	2 (1.3)	1 (0.6)	3 (1.0)	8 (1.1)	5 (0.7)	**19 (0.9)**
Protocol deviation	n (%)	2 (1.3)	-	1 (0.3)	5 (0.7)	5 (0.7)	**13 (0.6)**
Completed	**n (%)**	**125 (81.2)**	**131 (79.9)**	**229 (76.3)**	**477 (64.5)**	**458 (65.6)**	**1420 (69.1)**
In compliance with the protocol	n (%)	89 (57.8)	99 (60.4)	167 (55.7)	337 (45.6)	301 (43.1)	**993 (48.3)**
With a PD during the study	n (%)	36 (23.4)	32 (19.5)	62 (20.7)	140 (18.9)	157 (22.5)	**427 (20.8)**

% Percent of the Included Set
PD: Protocol Deviation

A total of 2055 patients having previously participated in either SOTI or TROPOS studies were included in the extension study. Out of them, 610 patients (29.7%) were withdrawn from the study. Patients from TROPOS were older than patients from SOTI, accounting for a higher rate of withdrawal (33.4% of withdrawals in patients from TROPOS, and 21.0% in patients from SOTI). However, patients from both studies (SOTI or TROPOS) were similarly affected by these withdrawals, whatever the treatment received before the inclusion in the extension study. Adverse events leading to treatment withdrawal were mainly: gastrointestinal disorders (43 events), nervous system disorders (41 events), neoplasms benign, malignant and unspecified (incl cysts and polyps) (32 events), and general disorders and administration site conditions (26 events).

Finally, most of the patients completed the study: 1420 patients (69.1% of the patients included).
Main baseline characteristics at inclusion in the extension study are summarised below.

Baseline characteristics at inclusion in the extension study in the included Set (N = 2055)

Parameters (unit)		**SOTI SR (N = 154)**	**SOTI SR/Placebo (N = 164)**	**SOTI Placebo/SR (N = 300)**	**TROPOS SR (N = 739)**	**TROPOS Placebo (N = 698)**
Total duration of SR treatment		8 years	7 years	4 years	8 years	3 years
Age (years)	Mean ± SD	72.9 ± 6.6	73.0 ± 6.6	72.8 ± 6.5	80.5 ± 4.4	80.6 ± 4.2
BMI (kg/m²)	Mean ± SD	26.93 ± 4.40	27.33 ± 4.53	26.84 ± 4.25	25.63 ± 4.42	25.58 ± 4.08
Time since menopause (years)	Mean ± SD	25.4 ± 7.9	26.3 ± 8.8	25.0 ± 7.8	32.1 ± 6.7	32.5 ± 7.1
L2-L4 BMD (g/cm^2)	Mean ± SD	0.853 ± 0.150	0.809 ± 0.140	0.756 ± 0.124	0.949 ± 0.205	0.814 ± 0.168
T-score	Mean ± SD	-2.252 ± 1.567	-2.707 ± 1.455	-3.263 ± 1.291	-1.247 ± 2.136	-2.659 ± 1.749
Prevalent vertebral fracture	n (%)	136 (88.31)	139 (84.76)	257 (85.67)	258 (34.91)	286 (40.97)
Previous peripheral fracture	n (%)	54 (35.06)	62 (37.80)	114 (38.00)	387 (52.37)	356 (51.00)

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SUMMARY – CONCLUSIONS (Cont'd)

At inclusion in the extension study, the age of patients was on average 78.2 ± 6.2 years. All patients were ambulatory.

Patients continuously treated with SR in SOTI or TROPOS had a higher BMD at inclusion in the extension study (lumbar, femoral neck or total hip BMD) than patients who were on placebo or who had a treatment switch to placebo at M48. Moreover, according to selection criteria based on lumbar BMD in SOTI and on femoral neck BMD in TROPOS, the highest mean values for lumbar BMD were observed in patients from TROPOS while the highest mean values for femoral neck BMD were observed in patients from SOTI.

In patients continuously treated with SR, mean BMD values in patients from SOTI were 0.853 ± 0.150 g/cm² for lumbar L2-L4 BMD, 0.650 ± 0.089 g/cm² for femoral neck BMD, and 0.778 ± 0.116 g/cm² for total hip BMD, and mean values in patients from TROPOS were 0.949 ± 0.205 g/cm² for lumbar L2-L4 BMD, 0.602 ± 0.074 g/cm² for femoral neck BMD, and 0.723 ± 0.099 g/cm² for total hip BMD.

The Sub FAS (patients from the FAS over 80) consisted of 822 patients, aged between 80 and 100 years (mean age: 83.6 ± 3.5 years).

The mean treatment duration during the extension, for all included patients was 2.7 years (31.6 ± 9.0 months, range0-45 months). For patients treated with SR since they were included in SOTI or TROPOS, the mean treatment duration reached 7.6 years (91.4 ± 9.5 months).

During the extension study, compliance was similar regardless of the SOTI or TROPOS group patients had belonged to (86.0 ± 16.7% in average, in the FAS).

EFFICACY RESULTS

Evolution of BMD in patients treated with SR for 8 years

Changes in BMD over the 8-year follow-up period in patients from the FAS treated with SR from the beginning of the SOTI or TROPOS studies are summarised in the table below.

Summary of changes in BMD during the first 5 years, the 3-year extension study and the 8-year follow-up in patients treated with SR for 8 years in the FAS

Changes (g/cm²) in		SOTI + TROPOS SR (N = 776)		
		During the 8-year follow-up (M0-End)	**During the first 5 years** (M0-M60)	**During the extension study (last 3 years)** (Baseline INCL-End)
Lumbar L2-L4 BMD	N	776	826	733
	Mean ± SD	0.204 ± 0.140	0.165 ± 0.118	0.041 ± 0.078
Femoral neck BMD	N	772	835	720
	Mean ± SD	0.057 ± 0.067	0.043 ± 0.050	0.013 ± 0.047
Total hip BMD	N	772	835	720
	Mean ± SD	0.069 ± 0.074	0.065 ± 0.059	0.007 ± 0.043

N: number of assessable patients
INCL: inclusion in the extension study

Evolution of BMD in patients treated with SR for 3 years

In patients from TROPOS placebo treated *de novo* with SR the last 3 years, the mean increases in BMD at each site were of the same order of magnitude as those reported in patients treated with SR over M0-M36.

Incidence of fractures in patients treated with SR for 8 years

The cumulative incidences of patients with at least one new osteoporotic fracture from the first SR intake (M0) to M96 was: vertebral or peripheral = 41.1%; peripheral = 24.7%; and vertebral = 27.4%. The incidence of vertebral and peripheral fractures was stable over the 8-year follow-up, and did not show the age-expected increase in incidence of fracture over the 3-year extension study, suggesting that the efficacy of SR persisted over time.

At each site, patients with a one-year active treatment interruption had a slightly higher cumulative incidence at M96 than patients with no interruption.

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SUMMARY – CONCLUSIONS (Cont'd)

Incidence of fractures in patients treated with SR for 3 years

In patients from the original TROPOS placebo group treated for 3 years with SR in the extension study, the cumulative incidence of patients with at least one new osteoporotic fracture from inclusion in the extension study to M96 was: vertebral or peripheral = 22.0%; peripheral = 12.0%; and vertebral = 15.1%.

The change in BMD and the incidence of osteoporotic fractures in **patients over 80** (SubFAS) showed the same trends as in the FAS, regardless of the original SOTI and TROPOS treatment groups, suggesting that efficacy of SR was maintained in elderly patients.

SAFETY RESULTS

The main safety results during the extension study in patients treated with strontium ranelate for 8 or 7 years are summarised below.

Main safety results

		SOTI + TROPOS SR (N = 892)	SOTI SR/placebo (N = 164)
Total duration of SR treatment		8 years	7 years
At least one emergent adverse event	n (%)	769 (86.2)	144 (87.8)
At least one treatment-related emergent adverse event	n (%)	26 (2.9)	6 (3.7)
At least one emergent adverse event leading to treatment stopped	n (%)	79 (8.9)	9 (5.5)
At least one emergent serious adverse event	n (%)	249 (27.9)	39 (23.8)
Treatment-related serious emergent adverse event	n (%)	3 (0.3)	-
Biological investigations			
At least one emergent CK value > 3 ULN	n (%)	-	-

** Percent calculated with respect to the total number of assessable patients*
ULN: upper limit of reference range

Emergent adverse events in patients treated with SR for 8 years

During the extension study, 769/892 patients from SOTI or TROPOS treated with SR for 8 years (*i.e.* 86.2%) presented at least one **emergent adverse event under treatment**. The most frequently affected system organ classes were musculoskeletal and connective tissue disorders (36.9% of these patients, mainly localised osteoarthritis: 9.9% and back pain: 7.0%), infections and infestations (32.6% of the patients, mainly urinary tract infection: 5.8%), vascular disorders (27.0%, mainly hypertension: 20.0%), gastrointestinal disorders (22.1%, mainly constipation: 3.5%, and diarrhoea: 2.7%), and nervous system disorders (22.0%, mainly sciatica 5.0%). The most frequently affected SOC during the extension study were similar to those previously described for patients treated with SR in the SOTI and TROPOS Phase III studies. However, in spite of the increasing age of patients, frequencies were lower during the extension study than in SOTI-TROPOS over M0-M36.

Among these events, 27 (in 2.9% of the patients) were considered **treatment-related** by the investigator. They concerned mainly gastrointestinal disorders (1.6% of the patients).

A total of 79/892 patients (8.9%) prematurely **discontinued the treatment** due to emergent adverse events, mainly related to gastrointestinal disorders (17 patients, 1.9%), nervous system disorders (13 patients, 1.5%) and neoplasms benign, malignant and unspecified (13 patients, 1.5%).

Adverse events observed in Phase III studies and mentioned in the current SPC as being more frequently reported in patients treated with strontium ranelate in comparison to placebo, were reported as follows:

- **Gastrointestinal disorders**: **diarrhoea** was reported in 2.7% of the patients, **nausea** in 0.9% of the patients and **loose stools** in 0.1% of the patients. These frequencies were lower than those observed in patients from SOTI and TROPOS treated with SR over 3 years (OSA report NP 08554): 6.5% for diarrhoea, 6.6% for nausea and 1.1% for loose tools, confirming previous findings that these events occur generally at the beginning of the SR treatment.

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SUMMARY – CONCLUSIONS (Cont'd)

- **Neurological disorders:** the frequency of **headache** was low: 0.7% of the patients, to be compared to 3.0% in the OSA report. For other neurological disorders, patients were less affected during the extension study than patients from SOTI or TROPOS over M0-M36 (OSA report) by **disturbance in consciousness** (1.2% *versus* 2.2% in the OSA report), and **seizure** (0.1% *versus* 0.3% in the OSA report), but more affected by **memory loss** (2.8% *versus* 2.1% in the OSA report).
- Skin affections like **dermatitis** or **eczema** affected less than 1% of the patients (*versus* 2.1% and 1.5%, respectively in the OSA report). It is of note that two cases of rash were reported in patients who initiated SR at the beginning of the extension study. Both were of moderate intensity and without any systemic symptoms.
- Regarding venous **thromboembolic events**, their occurrence in patients having performed the extension study was the same as that mentioned in the OSA report over M0-M36 *i.e.* 2.2%, despite the increasing age of the patients which is a major risk factor for occurrence of VTE.

Serious emergent adverse events

Overall, during the extension study, 537/2053 patients (*i.e.* 26.2% of the patients of the Safety Set) experienced at least one serious emergent adverse event under treatment patients from TROPOS being slightly more affected than patients from SOTI.

Regarding patients treated with SR for 8 years, 249/892 patients (*i.e.* 27.9% of the patients) were affected by at least one serious emergent adverse event during the extension study, mainly related to cardiac disorders (7.4% of the patients), nervous system disorders (4.8%), infections and infestations (4.7%), and neoplasms benign, malignant and unspecified (incl cysts and polyps) (4.4%). Most frequent serious adverse events reported were atrial fibrillation in 19 patients (2.1%), pneumonia in 11 patients (1.2%), deep vein thrombosis in 11 patients (1.2%), cardiac failure in 10 patients (1.1%), and cerebrovascular accident in 9 patients (1.0%).

Deaths

Overall**,** 86/2053 patients (*i.e.* 4.2%) from the Safety Set died during the extension study, with a higher frequency of death in patients previously included in TROPOS study, who were older than those included in SOTI study. The percentage of patients who died during the extension was comparable to that observed in previous Phase III studies (OSA report), in patients treated with SR over M0-M36 (*i.e.* 4.6%).

Deaths were mainly related to neoplasms (18 patients), cardiac disorders (15 patients, mainly acute myocardial infarction in 6 patients), general disorders and administration conditions (14 patients, mainly general physical health deterioration in 6 patients, and sudden deaths in 6 patients), infections and infestations (12 patients, mainly pneumonia in 5 patients), and nervous system disorders (9 patients, mainly cerebrovascular accident in 5 patients). In addition, 3 patients died from pulmonary embolism. All deaths were considered not treatment-related, except for one patient, dead from pancreatic carcinoma, for whom the relationship to treatment was impossible to say according to the investigator.

Laboratory safety tests

No clinically relevant changes over time were detected for **biochemistry** and **haematological parameters**, except CK (all values were < 3 ULN) and alkaline phosphatase increases. As observed in previous phase III studies, CK increase was dependent on the musculoskeletal fraction without increase in cardiac isoenzyme, and no increase in transaminases was detected. Results in patients over 80 led to similar conclusions.

Vital signs (weight, height, sitting systolic and diastolic blood pressure, heart rate)

No clinically relevant changes over time were detected.

Regarding **patients older than 80 years**, distribution and frequency of emergent adverse events obtained during the extension study were similar as compared to the whole population. However, frequency of serious emergent adverse events in patients over 80 years were similar to that reported in the overall TROPOS population.

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CONCLUSION

In the extension study, osteoporotic women who received strontium ranelate during the 5-year follow-up of SOTI or TROPOS were treated for an additional 3-year period. Most patients completed the extension period, and the compliance was satisfactory. During this additional 3-year period, the increase in lumbar BMD was 0.047 g/cm² while it was 0.165 g/cm² for the first 5-year, and 0.204 g/cm² for the whole 8-year follow-up period. The incidence of vertebral and peripheral osteoporotic fractures during the extension period did not show the age-expected increase. Results obtained in patients who received placebo during TROPOS then started the SR treatment at the entry in the extension study suggest a beneficial effect of SR even when initiated later in older patients.

The safety profile of strontium ranelate in patients treated for 8 years showed a good benefit/safety ratio and was in agreement with previous findings, with no occurrence of new safety signal during the extension study. Safety profile in patients over 80 was similar to that observed in the overall population. The frequency of adverse events attributable to strontium ranelate was similar or lower than that mentioned in the Summary of Product Characteristics.

Date of the report: 6 December 2007