Document title	**Clinical Study Synopsis Report**
Study title	**A prospective, controlled, double blind, international study to assess the effects of strontium ranelate *versus* placebo on the reduction of periprosthetic bone loss in patients with total hip arthroplasty** **The "Periprosthetic bone loss" study**
Study drug	**S 12911 (strontium ranelate)**
Studied indication	**Reduction of periprosthetic bone loss in patients with total hip arthroplasty for coxarthrosis**
Development phase	**Phase III**
Protocol code	**CL3-12911-037**
Study initiation date	**08 June 2011**
Study completion date	**26 April 2013**
Main coordinator	[redacted] [redacted] **Italy**
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex – France**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**01 April 2014**
Version of the report	**Final version**
	~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Protelos® / Osseor® / Protos® **Name of Active Ingredient:** Strontium ranelate (S 12911)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: A prospective, controlled, double blind, international study to assess the effects of strontium ranelate *versus* placebo on the reduction of periprosthetic bone loss in patients with total hip arthroplasty. The "Periprosthetic bone loss" study. Protocol No.: **CL3-12911-037** EudraCT Number: **2010-020215-36** The description of the study protocol given hereafter includes the modifications of the four substantial amendments to the protocol.		
International Coordinator: [redacted]; Italy.		
Study centres: 17 centres were opened in 5 countries and all included at least one patient: 6 centres in Italy (29 included patients), 2 centres in Germany (21 included patients), 1 centre in Belgium (5 included patients), 5 centres in Spain (29 included patients), and 3 centres in Brazil (12 included patients).		
Publication (reference): Not applicable.		
Studied period: Initiation date: 08 June 2011 Completion date: 26 April 2013	**Phase of development of the study:** III	
Objectives: ***Primary objective:*** To show the efficacy of strontium ranelate *versus* placebo in the reduction of periprosthetic bone loss in region 7 of Gruen, over 12 months of treatment after total hip arthroplasty (THA). ***Secondary objectives:*** - To show the efficacy of strontium ranelate *versus* placebo in the reduction of periprosthetic bone loss in: • The proximal femoral region of interest (proxROI) over 12 months of treatment. • The total region of interest (totROI) over 12 months of treatment. • Regions 1 to 6 of Gruen, respectively, over 12 months of treatment. - To assess the efficacy of strontium ranelate *versus* placebo on the same criteria described above over 6 months of treatment (removed by Amendment No. 4). - To assess the clinical and biological safety of strontium ranelate over 12 months of treatment.		
Methodology: This was a phase III, multicentre, international, prospective, randomised, double-blind study in 2 parallel arms over 12 months in patients with total hip arthroplasty (THA). Study treatments (strontium ranelate and placebo) were allocated at the inclusion visit (M0) using a balanced (non-adaptive) randomisation (ratio 1:1) stratified on centre. Patients received, during a 12-month treatment period, according to their randomisation group, either strontium ranelate (2 g) daily or placebo. A supplementation of 1000 mg calcium and 800 IU vitamin-D was provided to all patients. Periprosthetic Bone Mineral Density (BMD) was measured by Dual Energy X-ray Absorptiometry (DXA) at each visit from baseline to M12.		
Number of patients: Planned: 126 (63 by treatment group). Included in the Randomised Set: 96 (46 in the strontium ranelate (SrRan) group and 50 in the Placebo group). The number of included patients was lower than planned, as the recruitment was prematurely stopped by the sponsor, owing to a new contraindication of strontium ranelate (patients temporarily or permanently immobilized, included in Amendment No. 3).		

Diagnosis and main criteria for inclusion:
The study was performed in Caucasian males or post-menopausal females aged 50 years or more, 5 to 14 days after their THA, with:

- Conventional primary THA.
- Primary coxarthrosis as indication of THA.
- Cementless femoral stem.

Study drug:
One sachet daily containing 2 g of strontium ranelate, administered orally in the evening at bedtime, associated with calcium 1000 mg/day and vitamin D3 800 IU/day taken at breakfast.
Batch No.: L0034699; L0037524; L0040033; L0040486.

Comparator (Placebo):
One placebo sachet daily in the evening at bedtime, associated with calcium 1000 mg/day and vitamin D3 800 IU/day taken at breakfast.

Duration of treatment:
Run-in period: 5 to 21 days.
One-year active treatment period, with visits at M0, M3, M6 and M12.

Criteria for evaluation:

- ***Primary efficacy criterion:*** Periprosthetic BMD in region 7 of Gruen, assessed by DXA at M0, M3, M6 and M12.
- ***Secondary criteria:***
  - Efficacy:
    - Periprosthetic BMD in proximal femoral region of interest (proxROI, corresponding to the mean of periprosthetic BMD of region 1 and region 7 of Gruen).
    - Periprosthetic BMD in total region of interest (totROI, corresponding to the mean of periprosthetic BMD of the 7 regions of Gruen).
    - Periprosthetic BMD in region 1 to 6 of Gruen.
  - Safety: adverse events, clinical evaluation (blood pressure and heart rate, weight, BMI, physical examination), blood biochemistry and haematology.

Statistical methods:
Efficacy analysis:
The Full Analysis Set (FAS, main analysis set) included all randomised patients who took at least one dose of the study treatment and having at least one baseline and one post-baseline assessable BMD measurement in the region 7 of Gruen.

Primary criterion: periprosthetic BMD in region 7 of Gruen
Main analysis:
The main analytical approach was the relative change from baseline to the last assessable post-baseline value over 12 months (End). The comparison between strontium ranelate and placebo was performed in the FAS using a general linear model studying treatment effect, with pooled centre as covariate (pooled centre was considered as a fixed effect). Estimate of the difference between adjusted group means and Standard Error of the estimate (SE) were provided with its 95% Confidence Interval (CI) and the associated p-value.

Sensitivity analyses:

- The same analysis was performed in the PPS.
- Treatment groups were compared on the relative change from baseline to End using a general linear model adjusted on risk factors (pooled centre, age, sex, contralateral hip or lumbar spine T-score at baseline, time between THA and inclusion), in the FAS and the PPS.
- Treatment groups were compared on the relative change from baseline to End using a general linear model adjusted on risk factors after imputation of the missing T-scores (using a multiple imputation procedure), in the FAS and the PPS (complementary analysis).

Secondary analysis (in the FAS and the PPS):

- The same linear model as above (*i.e.* studying treatment effect with pooled centre as covariate) was applied on the relative change from baseline to each post-baseline visit.
- Treatment groups were compared on the relative change from baseline to each post-baseline visit using a general linear model adjusted on risk factors (pooled centre, age, sex, contralateral hip or lumbar spine T-score at baseline, time between THA and inclusion). Descriptive statistics were provided by treatment group for each visit until M12.

Statistical methods (Cont'd):

Secondary efficacy criteria:
Periprosthetic BMD in proxROI (mean of regions 1 and 7), totROI (mean of all regions), and regions 1 to 6 of Gruen: same analyses as for the primary efficacy criterion were performed in the FAS and the PPS.
In addition, for periprosthetic BMD in proxROI and region 1 of Gruen, treatment groups were compared on the relative change from baseline to End using a general linear model adjusted on risk factors after imputation of the missing T-scores (using a multiple imputation procedure), in the FAS and the PPS (complementary analysis).

Safety analysis:
Descriptive statistics were provided in the Safety Set: adverse events, laboratory parameters (biochemistry and haematology), and vital signs (blood pressure, heart rate, weight and BMI).

SUMMARY - CONCLUSIONS
STUDY POPULATION AND OUTCOME

A total of 98 patients were selected for the study, among whom 96 were included and randomly assigned to the SrRan (46 patients) group or Placebo group (50 patients). The number of included patients was lower than planned, as the recruitment was prematurely stopped by the sponsor.
Overall, 72.9% of the randomised patients completed the study and 27.1% were prematurely withdrawn. The rates of withdrawals for adverse events and non-medical reason were lower in the SrRan group (8.7% for both) than in the Placebo group (14.0% for both), whereas the rate of withdrawals for protocol deviation, required by the protocol, was greater in the SrRan group (8.7%) than in the Placebo group (none).

Disposition of patients according to treatment dispensed at inclusion

Status		SrRan	Placebo	All
Included and randomised	**N**	**46**	**50**	**96**
in compliance with the protocol	n (%)	32 (69.6)	34 (68.0)	66 (68.8)
with a protocol deviation before or at inclusion	n (%)	14 (30.4)	16 (32.0)	30 (31.3)
Withdrawn due to	n (%)	**12 (26.1)**	**14 (28.0)**	**26 (27.1)**
adverse event	n (%)	4 (8.7)	7 (14.0)	11 (11.5)
protocol deviation	n (%)	4 (8.7)	-	4 (4.2)*
non-medical reason	n (%)	4 (8.7)	7 (14.0)	11 (11.5)
Completed	n (%)	**34 (73.9)**	**36 (72.0)**	**70 (72.9)**
in compliance with the protocol	n (%)	28 (60.9)	33 (66.0)	61 (63.5)
with a protocol deviation during the study	n (%)	6 (13.0)	3 (6.0)	9 (9.4)

**Including 2 patients with a history of Venous ThromboEmbolism (VTE), 1 patient with a cemented hip prosthesis and 1 patient having taken estradiol.*
N Total number of patients included and randomised.
n number of patients in each category.
% = (n/N) x 100.

In the Randomised Set, patients had a mean age of 64.4 ± 8.3 years, with 29.2% aged 70 years or more, with no relevant difference between groups. The rate of males was slightly lower in the SrRan group (39.1%) than in the Placebo group (50.0%).
Patients were included on average 9.6 ± 3.9 days after THA. A total of 4 patients (2 in each group) previously received treatment likely to interfere with bone metabolism: calcium, combinations with vitamin D and/or other drugs (1 patient in the SrRan group *versus* 2 patients in the Placebo group), bisphosphonates (1 patient in the SrRan group *versus* 2 patients in the Placebo group), and vitamin D and analogues (1 patient in the Placebo group).
Mean periprosthetic BMD values at baseline were 1.23 ± 0.26 g/cm^2 in region 7 of Gruen, 0.86 ± 0.15 g/cm^2 in proximal femoral region of interest and 1.36 ± 0.19 g/cm^2 in total region of interest. No relevant difference between groups was observed for periprosthetic BMD values.

In the Randomised Set, the mean baseline contralateral femoral neck BMD was 0.888 ± 0.196 g/cm^2 without relevant difference between treatment groups. The mean lumbar spine BMD was 1.042 ± 0.206 g/cm^2, and tended to be slightly lower in the SrRan group (0.954 ± 0.152 g/cm^2) than in the Placebo group (1.159 ± 0.219 g/cm^2). The mean T-score was -0.45 ± 1.33, and was also lower in the SrRan group (-0.60 ± 1.19, median -0.70) than in the Placebo group (-0.32 ± 1.45, median -0.55).

SUMMARY – CONCLUSIONS (CONT'D)
STUDY POPULATION AND OUTCOME (Cont'd)

Over the M0-M12 period in the FAS, the mean treatment exposure was 314.1 ± 102.9 days (median 362.0 days, approximately 12 months), with no relevant between-group difference. In the Safety Set, the mean treatment exposure over M0-M12 was 304.5 ± 113.4 days (median 362.0 days, *i.e.* approximately 12 months). The mean compliance over the M0-M12 period was 85.3 ± 20.9%, without relevant difference between groups.

EFFICACY RESULTS

Primary assessment criterion: periprosthetic BMD in region 7 of Gruen
Relative change from baseline to last post-baseline value over M0-M12 (main analysis)
Over the M0-M12 period in the FAS, the mean relative change from baseline to the last post-baseline value in periprosthetic BMD in region 7 of Gruen was -14.90 ± 14.16% in the SrRan group and -16.56 ± 15.32% in the Placebo group, without statistically significant difference between groups (E (SE) = 1.44 (3.17)%, 95% CI = [-4.87 ; 7.76], p = 0.650). Same trends were observed for the sensitivity analysis adjusted on risk factors and by the analysis adjusted on risk facors after imputation of missing T-scores at baseline (complementary analysis).

In the PPS, same trends were observed for the mean relative change over M0-M12. After adjusting for risk factors, the estimate of the between group difference for relative change was slightly greater (E (SE) = 2.95 (5.20)%, 95% CI [-7.61 ; 13.51], p = 0.575). The estimate of the adjusted between-group difference after imputation of T-scores was E (SE) = 1.91 (4.90)% (95% CI = [-7.69 ; 11.52]; p = 0.696, complementary analysis).

Periprosthetic BMD in region 7 of Gruen – FAS (N = 83)
Relative change (%) from baseline to last post-baseline value over M0-M12 period

Periprosthetic BMD in region 7 of Gruen		**SrRan (N = 38)**	**Placebo (N = 45)**
Baseline (g/cm^2)	Mean ± SD	1.2085 ± 0.2794	1.2805 ± 0.1995
	Min - Max	0.676 ; 2.130	0.807 ; 1.769
End (g/cm^2)	Mean ± SD	1.0347 ± 0.3049	1.0721 ± 0.2784
	Min - Max	0.258 ; 2.048	0.484 ; 1.921
Relative change from baseline to End (%)	Mean ± SD	-14.90 ± 14.16	-16.56 ± 15.32
	Min - Max	-61.83 ; 11.34	-55.64 ; 9.44
Main Statistical analysis			
	E (SE)[1 1)]	1.44 (3.17)	
	95%CI[(2)]	[-4.87 ; 7.76]	
	p-value[(3)]	0.650	
Sensitivity analysis (adjustment on risk factors*)			
	E (SE)[1 2)]	1.87 (3.44)	
	95%CI[(2)]	[-5.00 ; 8.74]	
	p-value[(3)]	0.588	

Baseline value of DXA measurement obtained at any time between the selection and the inclusion visit (included).
End last reliable post baseline value over M0-M12.
(1.1) Estimate (Standard Error) of adjusted means difference SrRan - placebo (pooled centre as fixed effect).
(1.2) Estimate (Standard Error) of adjusted means difference SrRan - placebo (pooled centre, age, sex, contralateral hip or lumbar spine T-score at baseline and time between THA and inclusion as fixed effect).
(2) 95% Confidence Interval of the estimate.
(3) Corresponding p-value (Student t-test, general linear model).
** Some patients were not included in the analysis adjusted on risk factors as their contralateral hip or lumbar spine T-scores were missing.*

Relative changes from baseline to each post-baseline visit
The mean relative changes from baseline to each post-baseline visit in periprosthetic BMD in region 7 of Gruen did not statistically significantly differ between groups. Sensitivity analyses with adjustment on risk factors showed the same trends, with no statistically significant difference between groups.
Similar results were obtained in the PPS.

SUMMARY – CONCLUSIONS (CONT'D)
EFFICACY RESULTS (Cont'd)

Secondary criteria
Periprosthetic BMD in proximal femoral region of interest (proxROI)
Over M0-M12 in the FAS, the mean relative change in periprosthetic BMD in proxROI was lower in the SrRan group (-1.93 ± 14.11%) than in the Placebo group (-8.61 ± 9.66%), with statistical significance in favour of strontium ranelate (E (SE) = 6.74% (2.72), 95% CI [1.32 ; 12.16], p = 0.015). Analysis adjusted on risk factors showed the same trend without reaching the statistical significance (p = 0.082). The estimate of the adjusted between-group difference after multiple imputation of T-scores showed a statistically significant lower decrease in the SrRan group than in the Placebo group (E (SE) = 6.23 (2.75)%, 95% CI = [0.83 ; 11.62]; p = 0.024) (complementary analysis).

Results were similar in the PPS with an estimate of the between-group difference for relative change of 7.84% (3.45) (95% CI [0.89 ; 14.80], p = 0.028) that was confirmed by the analysis adjusted on risk factors (E (SE) = 7.47% (3.58), 95% CI [0.21 ; 14.74], p = 0.044), and by the analysis adjusted for risk factors after multiple imputation of T-scores (E (SE) = 7.65% (3.43), 95% CI [0.92 ; 14.38], p = 0.026, complementary analysis).

Periprosthetic BMD in total region of interest (totROI)
Over M0-M12 in the FAS, the mean relative change in periprosthetic BMD in totROI was 0.20 ± 7.24% in the SrRan group and -1.91 ± 5.29% in the Placebo group, without reaching statistical significance (E (SE) = 1.98% (1.40), 95% CI [-0.80 ; 4.76], p = 0.161). Results were confirmed by the analysis adjusted on risk factors and in the PPS.

Periprosthetic BMD in regions 1 to 6 of Gruen
Over M0-M12 in the FAS, the mean relative change in periprosthetic BMD in region 1 of Gruen was 5.42 ± 17.54% in the SrRan group *versus* -2.60 ± 12.24% in the Placebo group, with statistically significant difference in favour of strontium ranelate (E (SE) = 8.24% (3.40), 95% CI [1.47 ; 15.00], p = 0.018). This difference was considered as clinically significant.
The analysis adjusted on risk factors showed the same trend without reaching the statistical significance (E (SE) = 5.15% (3.31), 95% CI [-1.46 ; 11.75], p = 0.125). After imputation of the missing T-Scores at baseline, the estimate of the between-group difference (E (SE) = 7.14 (3.38)%, 95% CI [0.51 ; 13.77], complementary analysis) was higher than the planned adjusted analysis without imputation, with statistical significance in favour of strontium ranelate (p = 0.035).
Results were similar in the PPS with an estimate (SE) of the between-group difference for relative change of 10.84% (4.20) (95% CI [2.35 ; 19.33], p = 0.014). Same trends were obtained in the analysis adjusted on risk factors (E (SE) = 8.65% (4.23), 95% CI [0.06 ; 17.24], p = 0.048), and the analysis adjusted for risk factors after multiple imputation of T-scores (E (SE) = 9.95% (4.18), 95% CI [1.77 ; 18.14], p = 0.017) (complementary analysis).

Regarding regions 2 to 6 of Gruen, mean relative changes in BMD from baseline to the last post-baseline value over M0-M12 were, with no statistically significant difference between groups:
- Region 2 of Gruen: -1.83 ± 9.10% in the SrRan group *versus* -4.58 ± 8.25% in the Placebo group, E (SE) = 2.44% (1.84), 95% CI [-1.23 ; 6.11], p = 0.189.
- Region 3 of Gruen: 1.51 ± 6.94% *versus* 0.14 ± 9.74%, E (SE) = 1.36% (1.98), 95% CI [-2.58 ; 5.31], p = 0.493.
- Region 4 of Gruen: 1.71 ± 5.77% *versus* 1.02 ± 5.09%, E (SE) = 0.63% (1.20), 95% CI [-1.76 ; 3.03], p = 0.600.
- Region 5 of Gruen: 2.37 ± 9.20% *versus* 1.44 ± 6.90%, E (SE) = 0.83% (1.82), 95% CI [-2.79 ; 4.45], p = 0.650.
- Region 6 of Gruen: -2.16 ± 12.95% *versus* -3.38 ± 9.62%, E (SE) = 0.67% (2.43), 95% CI [-4.17 ; 5.51], p = 0.784.

Results were confirmed by the analysis adjusted on risk factors and showed the same trends in the PPS.

SUMMARY – CONCLUSIONS (CONT'D)

SAFETY RESULTS

- **Emergent adverse events**

Main safety results

		SrRan (N = 44)	Placebo (N = 47)
Patients having reported			
at least one emergent adverse event	n (%)	28 (63.6)	31 (66.0)
at least one treatment-related emergent adverse event	n (%)	7 (15.9)	7 (14.9)
Patients having experienced			
at least one serious emergent adverse event (including death)	n (%)	9 (20.5)	8 (17.0)
at least one treatment-related serious emergent adverse event	n (%)	-	-
Patients withdrawn from treatment			
due to an adverse event	n (%)	4 (9.1)	7 (14.9)
Patients who died	n (%)	-	1 (2.1)

The overall frequency of patients who reported at least one emergent adverse event showed no relevant difference between treatment groups: 28 patients (63.6%) in the SrRan group and 31 patients (66.0%) in the Placebo group.

The most frequent emergent adverse events, *i.e.* those reported by at least 2 patients in the SrRan group, were, with no particular preferred term affected:

- Diarrhoea: 2 patients in each group.
- Hip arthroplasty: 2 patients *versus* 1 patient, respectively.
- Osteoarthritis: 2 patients *versus* 1 patient, respectively.
- Device dislocation: 3 patients *versus* none, respectively.
- Vomiting: 3 patients *versus* none.
- Arthralgia: 2 patients *versus* none.
- Frequent bowel movements: 2 patients *versus* none.

Severe emergent adverse events were reported in 4 patients in each group (*i.e.* 9.1% in the SrRan group and 8.5% in the Placebo group). In the SrRan group, two patients reported severe device dislocation and two had severe hip arthroplasty. All these severe events were notified as serious and one (device dislocation) led to study drug withdrawal. None of the severe emergent adverse events reported in the SrRan group was considered as treatment-related by the investigator, and all were recovered.

A total of 9 patients (20.5%) in the SrRan group and 8 patients (17.0%) in the Placebo group (including the patient who died) experienced at least one serious emergent adverse event (SEAE). The most frequently affected system organ classes were:

- In the SrRan group: General disorders and administration site conditions (3 cases of device dislocation) and Musculoskeletal and connective tissue disorders (2 cases of osteoarthritis and 1 case of foot deformity).
- In the Placebo group: Infections and infestations (6 patients, 12.8%).

None of these SEAEs were considered as treatment-related by the investigator.

One patient with medical history of type 2 diabetes mellitus in the Placebo group died from an acute renal failure 69 days after drug withdrawal in a septic context (osteomyelitis bacterial, lung infection), with cardiac complications (congestive cardiomyopathy, cardiopulmonary failure, hypertension, coronary artery disease).

SUMMARY – CONCLUSIONS (CONT'D)

SAFETY RESULTS (Cont'd)

Emergent adverse events leading to premature discontinuation were less frequent in the SrRan group (4 patients, 9.1%) than in the Placebo group (7 patients, 14.9%), and were mainly related to:

- In the SrRan group: Gastrointestinal disorders (3 patients, 6.8%).
- In the Placebo group: General disorders and administration site conditions (3 patients, 6.4%) and Skin and subcutaneous tissue disorders (2 patients, 4.3%).

- **Laboratory tests**

Regarding biochemical parameters, the number of patients with emergent PCSA values was low in both groups: 1 patient in the SrRan group, with cholestasis at selection, had emergent PCSA value for ASAT, and 3 patients in the Placebo group had emergent PCSA values for ASAT, GGT and chloride, respectively. For haematological parameters, two patients had emergent PCSA values: 1 in the SrRan group had PCSA value for neutrophils (for which a retest performed 3 weeks later was considered as not clinically significant by the investigator) and one in the Placebo group had PCSA value for haematocrit.

- **Vital signs**

Clinical examination (weight, BMI, sitting blood pressures and heart rate) did not show any clinically relevant changes over time nor differences between groups.

CONCLUSION

In patients having undergone a total hip arthroplasty for osteoarthritis, this Phase III study could not show a reduction of the periprosthetic bone loss in region 7 of Gruen, following a 12-month treatment with strontium ranelate 2 g/day *versus* placebo. Nevertheless, a statistical significant reduction of the periprosthetic bone loss in favour of strontium ranelate *versus* placebo was observed in region 1 of Gruen, and in the proximal femoral region of interest (*i.e.* mean of regions 1 and 7), reaching clinical significance for region 1 of Gruen (mean relative change: E (SE) = 8.24% (3.40), 95% CI [1.47 ; 15.00], p = 0.018). These results suggested that the positive effect of strontium ranelate *versus* placebo in proximal femoral region of interest was driven by the effect observed in the region 1. Safety was in accordance with the known profile of strontium ranelate.

Date of the report: 01 April 2014

Version of the report: Final Version