Document Title	**Clinical Study Report Synopsis**
Study title	**Effects of strontium ranelate (2 g per day) in the management of long bone fractures with delayed union or non-union: an international open label study (as per Amendments No. 3 and No. 6)**
Study drug	**Strontium ranelate (S 12911)**
Studied indication	**Delayed and non-united fractures**
Development phase	**Phase III**
Protocol code	**CL3-12911-036**
Study initiation date	**25 June 2010**
Study completion date	**05 April 2013**
Main coordinator	[redacted] **France**
Sponsors	**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 final report	**Final version of 25 March 2014**

~~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®** **Name of Active Ingredient:** **Strontium ranelate** **(S 12911)**		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: Effect of strontium ranelate (2g per day) in the management of long bone fractures with delayed union or non-union: an international open label study (as per Amendments No.3 and 6) Protocol No.: CL3-12911-036 EudraCT No.: 2009-017039-16 The description of the study protocol given hereafter includes the modifications of the 9 substantial amendments to the protocol.		
International coordinator : [redacted] France		
Study centres: Multicentre study: 12 centres in 5 countries included 48 patients: Brazil (3 centres – 23 patients), Czech Republic (2 centres - 9 patients), Hungary (3 centres - 10 patients), Italy (1 centre – 1 patient), Romania (3 centres - 5 patients).		
Publication (reference): Not Applicable		
Studied period: Initiation date: 25 June 2010 Completion date: 5 April 2013	**Phase of development of the study:** **III except for Brazil (phase II)**	
Objective: To assess the effects of strontium ranelate 2g/day in the management of aseptic fractures of the limbs or clavicle with delayed union or non-union.		
Methodology: This was a phase III international, prospective, exploratory, open labelled study in patients with a fracture of the limbs or clavicle with a delayed union or a non-union receiving strontium ranelate 2g/day for 12 months. This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents. Two statistical analyses were carried out during the study according to the protocol. The first analysis was made when all patients had completed their M6 visit (considered as the main statistical analysis) and the final analysis when all patients had completed their M12 visit. Results when all patients had completed their M12 visit. Results after 6 months and after 12 months of treatment are the subject of the present report.		
Number of patients: Planned: 40 patients Included: 48 patients		
Diagnosis and main criteria for inclusion: Men aged at least 18 years or post-menopausal women, with menopause defined as 24 months of amenorrhea or bilateral ovariectomy, with a fracture of the upper or lower limb or clavicle with a delayed union, defined as an absence of radiological full union after 6 months according to investigator's opinion or non-union, defined as non-union for at least 6 months and no sign of radiological healing or bone reaction since at least 3 months. Patients had had to be ambulatory prior to the qualifying fracture.		
Test drug: **Strontium ranelate:** one sachet with granules of strontium ranelate 2 g once daily in the evening at bedtime. In addition, all patients received a supplementation of calcium 1000 mg/day and vitamin D 800 IU/day in 2 tablets of Calperos D3®. Batch No.: L0032704, L0041887		
Comparator (Reference product and/or placebo): Not applicable.		

Duration of treatment:

- Run-in period of 2 weeks without treatment (from ASSE to M0).
- Open-labelled treatment period of 12 months (from M0 to M12).

Criteria for evaluation:

No primary criterion had been defined for this exploratory study.

Efficacy measurements:

Radiographs at the fractured site

Radiographs of the fractured site were to be performed at all visits except at inclusion according to the usual procedure of the centre. At each visit, 2 radiographs with 2 different incidences, preferably 1 lateral and 1 anteroposterior views, were to be carried out.

The investigator evaluated radiological changes at each post-inclusion visit using the following 3-graded scale:

- No union: no radiological change from inclusion.
- Progress to union: a definite change from the inclusion radiograph, either with new subperiosteal bone, fuzziness across the fracture site or new bone peripherally across the fracture site.
- Union: at least a marked change from inclusion with thicker and denser bone across at least 3 out of the 4 cortices visible in two different radiological planes and fuzziness across the fracture site.

All radiographs were centrally re-red by two independent experts (Amendment No.9). The procedure of diagnosis was as follows:

- If the two independent central readers had the same diagnosis, it was taken into account for analysis regardless of investigator's one.
- If the two independent central readers had a different diagnosis on the fracture, the diagnosis taken into account for the analysis was the central reader's diagnosis corresponding to the investigator's one.
- If the 3 diagnoses were different, adjudication was performed by the two joint central readers.

Surgical re-intervention

The rate of re-interventions was to be recorded at all follow-up visits. This did not apply to interventions related to soft tissue or vascularization around the fracture. Patient with a re-intervention continued the treatment and the study. Any surgical intervention was forbidden during the first 6-month of the study unless any medical need according to the investigators opinion.

In case of a fracture of the lower limb:

- *Patient's ability to walk:* Rated by the investigator at all visits except at inclusion.
- *Parker mobility score: A*ssessed by the investigator at selection (on his mobility at selection and at the time of fracture), at M6 and M12 or last visit in case of premature discontinuation.
- *Lower limb questionnaire:* Rated by the patient at each visit from inclusion.

In case of upper limb or clavicle fractures:

- *Quick DASH:* Rated by the patient at each visit from inclusion.

All types of fracture:

- *Pain reported by the patient:* Rated by the patient at each visit from inclusion.
- *EQ-5D©:* Rated by the patient at each visit from inclusion.

Safety measurements:

Adverse events: At each visit from selection.

Clinical examination: Height was measured at selection. Weight, systolic and diastolic blood pressures and heart rate were measured at selection, M6 and M12 visits, or in case of premature discontinuation.

A physical examination was performed at selection, inclusion, M6 and M12 visits, or in case of premature discontinuation.

Laboratory tests: Blood samples were collected at selection and M12 visits or in case of premature discontinuation. The following parameters were assessed in local laboratories:

- Haematology: haemoglobin, haematocrit, erythrocytes, white blood cell count, platelets.
- Biochemistry: ASAT, ALAT, GGT, total ALP, blood creatinine, CPK. In case total CPK was above the upper value of the reference range, the isoenzymes fractions were to be measured.

Statistical methods:
Two statistical analyses were carried out during the study according to the protocol. The first analysis was made when all patients had completed their M6 visit (considered as the main statistical analysis) and the final analysis when all patients had completed their M12 visit. Results when all patients had completed their M12 visit. Results after 6 months and after 12 months of treatment are the subject of the present report.
Efficacy analyses were performed in the FAS defined as all eligible*, included patients having taken at least one dose of study treatment and who have performed at least one post-baseline radiography during the M0-M6/M12 period.
** a patient was considered eligible if the investigator and the central readers all confirmed that the fracture fulfilled the radiological selection criteria.*

Analyses of radiological endpoints
The radiological state at the fractured site assessed by radiography as union, progress to union, or failure to union, was presented using descriptive statistics. The 95% confidence interval of the proportion of patient having a radiological state evaluated as 'Progress to union' or 'Union' was provided based on a binomial distribution.
Time to progression was studied using the Kaplan Meier method with the corresponding 95% confidence interval calculated using Greenwood's variance at each visit during M0-M6/M12 period.

Analyses of clinical endpoints
Lower limb score for patients with lower limb fractures and the QuickDASH score for patients with upper limb fractures, pain intensity score, EQ-5D© index and score were described at each visit using descriptive statistics and the change and relative change from baseline to each post-baseline visit using a two-tailed Student's t-test for paired samples providing the estimate (standard error) of the change / relative change, 95% CI and the associated p-value.
The rate of secondary surgical interventions during M0-M6/M12 period was also analysed with descriptive statistics and the time to secondary surgical intervention was assessed using the Kaplan Meier method with the corresponding 95% confidence interval calculated using Greenwood's variance.
In addition, for patients with lower limb fractures, statistical tests were used to study the time to full recovery (according to ability to walk) using the Kaplan Meier method with the corresponding 95% confidence interval calculated using Greenwood's variance, and the improvement in mobility with the change / relative change in Parker score from baseline to each post-baseline visit using a two-tailed Student's t-test for paired samples providing the estimate (standard error) of the change / relative change, 95% CI and the associated p-value.

Safety analyses: descriptive statistics in the Safety Set over M0-M12

SUMMARY - CONCLUSIONS
STUDY POPULATION AND OUTCOME

		S12911 2g
Included	N	48
Withdrawn due to	**n (%)**	**5 (10.4)**
- adverse event		1
- non-medical reason		3
- protocol deviation		1
Completed	**n (%)**	**43 (89.6)**
Full Analysis Set (FAS)	**n (%)**	**40 (83.3)**
Safety set	**n (%)**	**47 (97.9)**

% according to number of included patients

A total of 53 patients were selected for the study. Among them, 48 patients were included.
During the M0-M6 treatment period, 4 patients (8.3%) were prematurely withdrawn from the study, and 44 patients (91.7%) attended the M6 visit. After M6 up to M12, one more patient was prematurely withdrawn from the study. At M12, 43 patients (89.6%) completed the study.

In the Included Set, the patients were aged from 19 to 83 years (mean ± SD = 49.4 ± 18.5 years). Twenty-eight patients (58.3%) were males and 20 patients (41.7%) were females. All women were post-menopausal for 20.7 ± 12.9 years on average.
At selection, the weight ranged between 49.0 kg and 120 kg with a mean of 73.4 ± 17.6 kg, and the BMI ranged between 17.7 kg/m^2 and 40.3 kg/m^2 with a mean of 27.2 ± 5.5 kg/m^2.

SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Characteristics of qualifying fractures

At selection, the qualifying fractures occurred between 6 to 133 months ago, and 22.8 ± 27.5 months on average (median 12.5 months).

At selection, the qualifying fractures were diagnosed as non-union in 29 patients (60.4%), and delayed union in 19 patients (39.6%) according to radiological criteria.

The fracture most commonly affected lower limb (34 patients, 70.8%) including femur in 21 patients (43.8%) and tibia in 13 patients (27.1%). The other fractures affected humerus in 9 patients (18.8%) and other upper limb or clavicle in 5 patients (10.4%).

Fractures were mainly localized at bone shaft such as femoral shaft (17 patients, 35.4%) then tibial or humerus shafts (8 patients, 16.7%, and 7 patients, 14.6%, respectively).

Multiple fractures were reported in 21 patients (43.8%). Associated joint injury was reported in 9 patients (18.8%).

In 30 patients (62.5%), the fracture was related to high energy trauma.

At the time of fracture, the qualifying fracture was multifocal in 14 patients (29.2%). It was an open fracture in one quarter of patients (12 patients). The fracture was mainly transversal (20 patients, 41.7%), then comminutive (15 patients, 31.3%) and spiroid (13 patients, 27.1%). In most patients, the fractures were displaced (31 patients, 64.6%).

Previous conservative treatments were closed reduction in 10 patients (20.8%), and orthopaedic cast or splint in half patients (24 patients).

Initial surgical treatments were external fixation in 10 patients (20.8%), intramedullary nail in 13 patients (27.1%), and plate fixation 19 patients (39.6%). Revision of fixation was documented in 31/48 patients (64.6%).

History of fractures (excluding the qualifying one)

In the Included Set, 29 patients (60.4%) had a history of fracture. In all, 22 patients (45.8%) had previous fractures of the lower limb, mainly femur (17 patients, 35.4%), 16 patients (33.3%) had upper limb or clavicle fracture, and 8 patients (16.7%) had other fractures, of which 6 vertebral fractures.

Diagnosis of osteoporosis

At selection, 22/41 patients (53.7%, 7 patients without diagnosis) had a diagnosis of osteoporosis. Osteoporosis lasted for 20.5 ± 38.4 months on average. The longest duration was 113 months.

Among these patients, 17 patients (77.3%) had a BMD T-score (assessed by DXA) ≤ -2.5 SD at either the lumbar spine or total hip or femoral neck, and 5 (22.7%) had a BMD T-score ≤ -1 SD at either the lumbar spine or total hip or femoral neck with an osteoporotic fracture (the qualifying fracture may be considered as osteoporotic fracture if it is caused by an inadequate trauma).

Before study, 9 patients (18.8%) had been receiving at least one osteoporotic treatment or treatment related to bone metabolism. These treatments were vitamins D and analogues, calcium, drugs affecting bone structure and mineralization in 5 patients each (10.4%), and calcitonin preparations in 3 patients (6.3%).

In the Included Set, the total exposure duration ranged between 0 and 7.3 months with a mean (± SD) of 5.8 ± 1.2 months over M0-M6, and between 0 and 12.5 months with a mean (± SD) of 11.4 ± 2.4 months over M0-M12. Similar results were reported in the FAS and Safety Set over both periods. The mean duration of total exposure was similar regardless of fracture localisation over both periods.

During the study, all patients (not documented in one patient) daily took calcium and vitamin D in the Included Set. Most patients took between 900 mg/d and 1100 mg/d of calcium and 720 IU/d and 880 IU/d of vitamin D (96.3%, and 80.9% over M0-M6/M12).

One quarter of patients (25.0%) had 16 protocol deviations before or at inclusion. The most frequent deviation concerned radiographs at the fracture site not performed at the selection visit (9 patients, 18.8%, with one deviation). After inclusion up to M12, 7 patients (14.6%) had 14 protocol deviations. The most frequent deviation concerned radiographs at the fracture site not performed at one visit and at least one blood sample not taken at the last study visit (4 patients, 8.3%, with one deviation for each type).

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

- **Fracture radiological state**

In the FAS, healing progression (defined as progress to union or union) was reported in 70.0% of patients (95% CI [53.5-83.4]%, 28 patients) at the last post-baseline assessment over the M0-M6 period and 72.5% (95% CI [56.1-85.4]%, 29 patients) at the last post-baseline assessment over the M0-M12 period.
In the FAS, 35.0% of patients (14 patients) had union at the last post-baseline assessment over the M0-M6 period, and 3 more patients had union (17 patients, 42.5%) over the M0-M12 period.
The frequency of healing progression was similar whatever the type of disturbance healing (delayed union/non-union) or fracture location (lower limb/upper limb or clavicle).

In the FAS, healing progression of fractures mainly occurred within the first 2 months of treatment (22/29 patients with progression). The estimated (SE) incidence of progression at M2 was 55.0% (7.9%), 95% CI [39.6 – 70.4]%. At M6, it reached 71.1% (7.3%), 95% CI [56.8 – 85.5]%, and was very closed at M12 (74.3% (7.2%), 95% CI [60.3 – 88.4]%).
The time to healing progression was earlier for delayed union fractures than for non-union fractures, and was similar for upper limb or clavicle fractures and lower limb fractures.

- **Clinical criteria**
  - **Surgical re-intervention**

As recommended in the protocol, surgical re-interventions were avoid within the first 6 months of treatment:

- 2 patients (5.0%, 95% CI [0.6 – 16.9]%) during the M0-M6 period.
- 8 patients (20.0%, 95% CI [9.1 – 35.6]%) during the M0-M12 period, including the two patients cited above.

  - **Ability to walk**

In the FAS patients with lower limb fractures (N = 30), the incidence of patients fully recovered (walking without help) progressively increased throughout the M0-M12 period from 13.0% (7.0%), 95% CI [0.0 - 26.8]% within the first 2 months to 30.4% (9.6%), 95% CI [11.6 – 49.2]% at M6, and to 47.8% (10.4%), 95% CI [27.4 – 68.2]% at M12.

  - **Parker mobility score**

In the FAS patients with lower limb fractures (N = 30), the mean Parker mobility score remained stable between the baseline and M6 (mean change: 0.7 (0.4), 95 % CI [-0.0 – 1.4], p = 0.060). However, the corresponding mean relative change was statistically significant (18.9% (8.7%), 95 % CI [1.2 – 36.7]%, p = 0.037).
Between the baseline and M12, the mean Parker mobility score increased. This mean increase and the corresponding mean relative increase were both statistically significant (1.1 (0.4), 95 % CI [0.3 – 1.9], p = 0.007, and 27.1% (9.7%), 95 % CI [7.3 – 46.9]%, p = 0.009).

  - **VAS pain**

In the FAS, the mean decrease from baseline in VAS pain score was statistically significant at each visit and the last-post baseline assessment over the M0-M6 and M0-M12 periods, *e.g.*:

- At the last-post baseline assessment over M0-M6: -18.6 mm (3.6 mm), 95% CI [-25.9 - -11.4] mm, p < 0.0001.
- At the last-post baseline assessment over M0-M12: -21.5 mm (3.3 mm), 95% CI [-28.2 - -14.8] mm, p < 0.0001.

In the FAS, 48.7% of patients (19 patients) had a pain decrease by more than 50% at the last post-baseline assessment over M0-M6 compared to baseline, and 64.1% (25 patients) at the last post-baseline assessment over M0-M12.

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

According to baseline characteristics of fracture, results in the FAS patients with non-union fracture (N = 26) were similar to the results in the FAS. In the FAS patients with delayed union fracture (N = 14), the mean decrease from baseline in VAS pain score was statistically significant from M6 onwards and at both last-post baseline assessments, *e.g.*:

- At the last-post baseline assessment over M0-M6: -11.1 mm (5.0 mm), 95% CI [-21.9 - -0.4] mm, p = 0.0432.
- At the last-post baseline assessment over M0-M12: -21.4 mm (4.8 mm), 95% CI [-31.8 - -11.1] mm, p = 0.0006.

In the FAS patients with lower limb fractures (N = 30), results were in the same line as those observed in the FAS. In the FAS patients with upper limb or clavicle fractures (N=10), the mean decrease from baseline in VAS pain score was statistically significant at M4 and M6 and at the last-post baseline assessment over the M0-M6 period (-12.7 mm (5.0 mm), 95% CI [-23.9 - -1.5] mm, p=0.0304 for the last-post baseline assessment).

- **EQ-5D questionnaire**

In the FAS, the mean increase from baseline in EQ-5D index was statistically significant at each visit and the last-post baseline assessment over the M0-M6 and M0-M12 periods, *e.g.*:

- At the last-post baseline assessment over M0-M6: 0.126 (0.030), 95% CI [0.065 - 0.187], p = 0.0002.
- At the last-post baseline assessment over M0-M12: 0.227 (0.037), 95% CI [0.152 - 0.301], p < 0.0001.

In the FAS, the mean EQ-5D VAS score increased between the baseline and the last-post baseline assessment over the M0-M6 and M0-M12 periods. This increase was statistically significant over M0-M12 only (8.40 (4.11), 95% CI [0.08 - 16.72], p = 0.0479 at the last-post baseline assessment).

- **Lower limb questionnaire**

In the FAS patients with lower limb fractures (N = 30), the mean increase from baseline in lower limb standardised score was statistically significant at each visit and the last-post baseline assessment over the M0-M6 and M0-M12 periods, *e.g.*:

- At the last-post baseline assessment over M0-M6: 13.5 (2.1), 95% CI [9.3 – 17.7], p < 0.0001.
- At the last-post baseline assessment over M0-M12: 17.2 (1.9), 95% CI [13.4 – 21.1], p < 0.0001.

- **QuickDASH questionnaire**

In the FAS patients with upper limb or clavicle fractures (N = 10), the mean decrease from baseline in QuickDASH score was statistically significant at all visits but M2 and M9 and the last-post baseline assessment over the M0-M6 and M0-M12 periods, *e.g.*:

- At the last-post baseline assessment over M0-M6: -19.5 (4.9), 95% CI [-30.6 – -8.4], p = 0.0032.
- At the last-post baseline assessment over M0-M12: -20.2 (6.7), 95% CI [-35.4 – -5.05], p = 0.0146.

SUMMARY – CONCLUSIONS (Cont'd)
SAFETY RESULTS

- **Emergent adverse events**

Overall summary of adverse events during the M0-M12 period

		S12911 2g (N = 47)
Patients having reported		
at least one emergent adverse event	n (%)	19 (40.4)
at least one treatment-related emergent adverse event	n (%)	3 (6.4)
Patients having experienced		
at least one serious adverse event (including death)	n (%)	6 (12.8)
at least one serious emergent event (including death)	n (%)	6 (12.8)
at least one treatment-related serious adverse event	n (%)	-
Patients with treatment withdrawal		
due to an adverse event	n (%)	1 (2.1)
due to a serious adverse event	n (%)	1 (2.1)
due a treatment-related adverse event	n (%)	-
due a treatment-related serious adverse event	n (%)	-
Patients who died	n (%)	1 (2.1)*

** Sepsis following gunshot wound in abdominal area*

During the M0-M12 period, 19 patients (40.4%) of the Safety Set reported at least one emergent adverse event. The system organ classes affected in at least 10% of patients were infections and infestations (12 patients, 25.5%), and musculoskeletal and connective tissue disorders (6 patients, 12.8%).

The most frequent emergent adverse event was diarrhoea reported in 6.4% of patients (3 patients). Then, excluding infections, there were anaemia, arthralgia, fall, and pain in extremity, each reported in 4.3% of patients (2 patients). No venous or pulmonary thromboembolism, no myocardial infarction, no serious skin disorders were reported.

Excluding one patient shot in abdominal area, 4 severe emergent adverse events were reported in 3 patients (6.4%) (One fall leading to one femur fracture, one pseudoarthrosis on the non-target leg, one muscle atrophy). None was considered related to the study treatment by the investigator.

During the M0-M12 period, 3 patients (6.4%) experienced at least one emergent adverse event considered to be related to the treatment (diarrhoea in each patient, and in one patient pruritus generalised recovered on treatment followed by a new pruritus recovered on treatment).

During the M0-M12 period, one patient died of sepsis following gunshot wound in abdominal area.

Furthermore, 5 patients (10.6%) experienced at least one non-fatal emergent serious adverse event: fractures consecutively to falls in two patients (femur fracture in one patient, and pubis and sacrum fractures in the other patient), pseudoarthrosis in the non-target leg, and removal of internal fixation, both related to previous fractures in one patient each, and orchitis. None of these serious emergent adverse events were considered to be related to the study treatment by the investigator. All patients recovered.

No patient was prematurely withdrawn from the study treatment due to adverse event to the exclusion of patient shot.

SUMMARY – CONCLUSIONS (Cont'd)
SAFETY RESULTS (Cont'd)

- **Laboratory tests**
  Biochemistry
  During the M0-M12 period, 2 emergent PCSA high values were reported in 2 patients who already had abnormal values at selection: 1 CPK value (1165 IU/L, 4.0 ULN) in patient suffering from dengue, and 1 GGT value (364 IU/L, 9.1 ULN) reported as alcohol abuse.
  Haematology
  During the M0-M12 period, when excluded the patient shot, one patient had emergent PCSA low values of haematocrit (0.28) and red blood cell count (2.87 T/L) with haemoglobin value below the lower limit of reference range without reaching PCSA limit (93 g/L). These abnormal haematological parameters were related to "surgery: new plate" for the qualifying fracture. No further test was performed.

- **Vital signs**

During the M0-M12 period, no clinically relevant changes in weight and BMI, systolic and diastolic blood pressures, and heart rate (sitting position) were reported between the baseline and the last value on treatment.

CONCLUSION

This prospective exploratory open-labelled study conducted in patients with aseptic fractures of the limbs or clavicle with delayed union or non-union showed that 70.0% of FAS patients had healing progression (defined as progress to union or union) after 6 months of strontium ranelate 2 g/day whatever the type of disturbance healing (delayed union/non-union) or fracture location (lower limb/upper limb or clavicle).

In line with healing results, a statistically significant improvement in mobility was reported in patients with lower limb fractures, from 6 months of treatment onwards. In the same way, a statistically significant improvement in ability to do daily activities in patients with upper limbs or clavicle fractures as well as in pain, and quality of life in all patients was observed according to patients' judgment.

The safety profile of strontium ranelate 2g/day over 12 months was consistent with the listed events. No venous or pulmonary thromboembolism, no myocardial infarction, no serious skin disorders were reported.

Date of the report: 25 March 2014

Version of the report: Final version