Document title	**Clinical Study Report Synopsis**
Study title	**Long-term effects of strontium ranelate on knee osteoarthritis symptoms. A 2-year prospective randomised, placebo-controlled study.**
Study drug	**Strontium ranelate (S 12911)**
Studied indication	**Osteoarthritis**
Development phase	**Phase III**
Protocol code	**CL3-12911-028**
Study initiation date	**30 November 2006**
Study completion date	**25 January 2010**
Main coordinator	[redacted] **Belgium**
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	**Final version of 14 April 2011**

~~CONFIDENTIAL~~

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)*
Name of Finished Product: Protos®	**Volume:**	
Name of Active Ingredient: Strontium Ranelate (S 12911)	**Page:**	

Title of study: Long-term effects of strontium ranelate on knee osteoarthritis symptoms. A 2-year prospective randomised, placebo-controlled study.
Protocol No.: CL3-12911-028; Eudract number 2006-004194-10

Investigator:
[redacted] Belgium

Study centre: [redacted]
[redacted] Belgium.

Publication: None

Studied period: Initiation date: 30 November 2006 Completion date: 25 January 2010	**Phase of development of the study:** III

Objective: To assess the effectiveness of a 2-year treatment with strontium ranelate on algofunctional symptoms of knee osteoarthritis, compared to placebo.

Methodology:
Randomised, double-blind, 2 parallel groups, placebo-controlled trial

Number of patients:
Planned: 140 patients (for each group: 70 patients)
Included: 43 patients

Diagnosis and main criteria for inclusion:
Caucasian, ambulatory male or female patients aged 45 years or more, with primary knee osteoarthritis based on clinical and radiological criteria of the American College of Rheumatology.

Study drug:
S 12911 sachet containing 2 g of active principle, to be taken orally as a suspension once daily at bedtime.

Reference product:
Placebo sachet taken as a suspension once daily at bedtime

Duration of treatment: 2 years

Criteria for evaluation:
Efficacy measurements:
Primary efficacy endpoint:
Algofunctional assessment of the target knee (measured with the Lequesne index) at M0, M3, M6, M12, M18 and M24.
Secondary efficacy endpoints:

- Algofunctional WOMAC (Western Ontario and Mc Master Universities Osteoarthritis Index) index (Visual Analog Scale (VAS) version) at M0, M3, M6, M12, M18 and M24.
- Algofunctional COAT (Comprehensive OsteoArthritis index Test) index at M0, M3, M6, M12, M18 and M24.
- Radiographic assessment of the Joint Space Narrowing (JSN) by measuring the mean change in the minimal Joint Space Width (JSW) of the medial tibio-femoral compartment of the signal articulation at M0 and M24. A standardised radiographic anatomic positioning of the knee was used (postero-anterior, weight bearing, fixed-flexion radiography using a specially designed positioning frame (Synflaxer)).
- Knee physical examination at M0, M3, M6, M12, M18 and M24.
- Permitted pain medications or NSAID consumption during the study (used for pain-relief recorded by the use of a patient's diary).

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)*
Name of Finished Product: Protos®	**Volume:**	
Name of Active Ingredient: Strontium Ranelate (S 12911)	**Page:**	

Criteria for evaluation (Cont'd):
Safety measurements:

- Clinical examination (including blood pressure, heart rate, weight, height) at each visit.
- Assessment of adverse events at each visit.
- Assessment of biological parameters at selection and M24.

Statistical methods:
Due to poor recruitment leading to a limited sample size, no statistical testing was performed. Instead, all analyses were descriptive.

SUMMARY - CONCLUSIONS
STUDY POPULATION AND OUTCOME
Overall disposition of patients is summarised below.

Disposition of randomised patients

Status		**S 12911 (N = 22)**	**Placebo (N = 21)**	**All (N = 43)**
Included (randomised)	n	**22**	**21**	**43**
In compliance with the protocol	n (%)	22 (100.0)	20 (95.2)	42 (97.7)
With a protocol deviation at inclusion	n (%)	-	1 (4.8)	1 (2.3)
Withdrawn due to	n (%)	**6 (27.3)**	**4 (19.0)**	**10 (23.3)**
Adverse event	n (%)	4 (18.2)	1 (4.8)	5 (11.6)
Lack of efficacy	n (%)	1 (4.5)	1 (4.8)	2 (4.7)
Non-medical reason	n (%)	-	2 (9.5)	2 (4.7)
Lost to follow-up	n (%)	1 (4.5)	-	1 (2.3)
Completed	n (%)	**16 (72.7)**	**17 (81.0)**	**33 (76.7)**
In compliance with the protocol	n (%)	13 (59.1)	9 (42.9)	22 (51.2)
With a protocol deviation during the study	n (%)	3 (13.6)	8 (38.1)	11 (25.6)

A total of 43 patients were included and randomised in the study: 22 patients in the S 12911 group and 21 patients in the placebo group. Due to poor recruitment, the planned number of patients (70 patients by group) was not reached. At the M24 visit, 33 patients (76.7% of the randomised patients) completed the study: 16 patients (72.7%) in the S 12911 group and 17 patients (81.0%) in the placebo group.
One patient (4.8%) in the placebo group had a deviation at inclusion (unauthorised treatment: doxycycline). During the study, 20 patients (46.5%) presented 31 protocol deviations: 9 patients (40.9%) in the S 12911 group, and 11 patients (52.4%) in the placebo group. Deviations during the study mainly concerned overall compliance < 80%, unauthorised treatments and missing assessments (6 patients each).

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)*
Name of Finished Product: Protos®	**Volume:**	
Name of Active Ingredient: Strontium Ranelate (S 12911)	**Page:**	

SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Main baseline characteristics are summarised below.

Mean baseline characteristics in the Randomised Set

Parameter (unit)		**S 12911 (N = 22)**	**Placebo (N = 21)**	**All (N = 43)**
Age (years)	Mean ± SD	62.8 ± 6.6	61.6 ± 9.1	62.2 ± 7.8
	Min - Max	52 - 74	52 - 84	52 - 84
BMI (kg/m^2)	Mean ± SD	30.6 ± 5.0	29.3 ± 4.5	29.9 ± 4.8
	Min - Max	24.0 - 44.9	22.2 - 41.7	22.2 - 44.9
Lequesne index (global score)	Mean ± SD	9.8 ± 4.2	11.2 ± 3.9	10.5 ± 4.1
	Min - Max	2.5 - 20.0	2.0 - 18.5	2.0 - 20.0
WOMAC index (global score)	Mean ± SD	129.6 ± 70.6	159.3 ± 59.4	144.1 ± 66.3
	Min - Max	10.6 - 288.4	29.2 - 253.8	10.6 - 288.4
COAT index (global score)	Mean ± SD	48.5 ± 24.1	59.0 ± 19.2	53.6 ± 22.2
	Min - Max	7.5 - 90.3	11.0 - 89.3	7.5 - 90.3
Joint Space Width (mm)	Mean ± SD	2.1 ± 1.6	2.8 ± 1.9	2.5 ± 1.8
	Min - Max	0.0 - 5.0	0.0 - 6.4	0.0 - 6.4
Physical assessment of target Knee				
Swelling	n (%)	3 (13.6)	3 (14.3)	6 (14.0)
Warmth	n (%)	2 (9.1)	1 (4.8)	3 (7.0)
Effusion	n (%)	-	-	-

Age of randomised patients ranged from 52 to 84 years with a mean ± SD of 62.2 ± 7.8 years; 20 patients (46.5%) were male and 23 patients (53.5%) were female. All patients were ambulatory. Current smoking habits were reported by 3 patients (13.6%) in the S 12911 group and 4 patients (19.0%) in the placebo group.

Medical history included mainly osteoarthritis (other than knee osteoarthritis: 93.0%), hypertension (44.2%), menopause (41.9%) and hypercholesterolaemia (37.2%). The most frequent treatments at inclusion were analgesics (62.8%), anti-inflammatory and antirheumatic products (48.8%) and psycholeptics (32.6%).

All patients had knee osteoarthritis. The osteoarthritis was bilateral in about 3/4 of the patients. The disease duration ranged between 7 and 377 months with an average of 120.7 ± 97.3 months and was in average shorter in the S 12911 group than in the placebo group (92.6 months *versus* 150.2 months, respectively). All patients had knee pain during the previous month.

Baseline characteristics were similar in the two treatment groups except baseline values for Lequesne index, WOMAC index and COAT index which were in average lower in the S 12911 group than in the placebo group.

The mean duration of treatment was 21.6 ± 5.7 months. Global compliance was satisfactory, ranging between 70% and 130% in 92.3% of the patients.

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)*
Name of Finished Product: Protos®	**Volume:**	
Name of Active Ingredient: Strontium Ranelate (S 12911)	**Page:**	

SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Primary assessment criterion: Lequesne index in the FAS

Change from baseline to last value

The mean change in global score of Lequesne index was -0.9 ± 3.9 in the S 12911 group and -2.3 ± 6.2 in the placebo group.

Lequesne index (total score) Change from baseline to last value in the FAS

Total score of Lequesne Index		**S 12911 (N = 22)**	**Placebo (N = 21)**
Baseline	Mean ± SD	9.8 ± 4.2	11.2 ± 3.9
	Min - Max	2.5 - 20.0	2.0 - 18.5
End	Mean ± SD	8.9 ± 6.2	9.0 ± 5.4
	Min - Max	0.0 - 21.0	1.0 - 19.0
Change from baseline to End	Mean ± SD	-0.9 ± 3.9	-2.3 ± 6.2
	Min - Max	-7.5 - 7.5	-13.0 - 8.5

Change from baseline to each visit

The global score, the "pain" and the "activity of daily living" subscores of the Lequesne index tended to decrease from baseline to each visit in both groups, while the "maximum walked" subscore slightly increased in both groups.

Secondary criteria

The mean change in global score of WOMAC index was -36.81 ± 65.05 in the S 12911 group and -60.68 ± 91.45 in the placebo group. No relevant between-group differences were detected for the global score and each subscore of the WOMAC index.

WOMAC index (total score) Change from baseline to last value in the FAS

Total score of WOMAC index		**S 12911 (N = 22)**	**Placebo (N = 21)**
Baseline	Mean ± SD	129.63 ± 70.65	159.25 ± 59.38
	Min - Max	10.63 - 288.43	29.21 - 253.84
End	Mean ± SD	92.83 ± 79.23	98.57 ± 77.94
	Min - Max	0.65 - 252.89	10.63 - 263.98
Change from baseline to End	Mean ± SD	-36.81 ± 65.05	-60.68 ± 91.45
	Min - Max	-180.85 - 100.24	-209.56 - 132.51

The algofunctional COAT index decreased in both groups, from 48.46 ± 24.07 at baseline to 36.34 ± 29.97 at last evaluation in the S 12911 group and from 59.04 ± 19.20 to 38.92 ± 28.94 in the placebo group.

The joint space width decreased in both groups: -0.05 ± 0.22 mm in the S 12911 group and -0.16 ± 0.25 mm in the placebo group.

Pain flares occurred in 54.3 ± 35.7% of days in the S 12911 group and 57.1 ± 38.4% of days in the placebo group. Consumption of analgesics occurred in 27.3 ± 30.0% of the days in the S 12911 group and in 21.1 ± 27.6% of the days in the placebo group.

Considering the small number of patients included in the study, no conclusion could be drawn regarding the effect of S 12911 on the algofunctional symptoms in knee osteoarthritis.

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)*
Name of Finished Product: Protos®	**Volume:**	
Name of Active Ingredient: Strontium Ranelate (S 12911)	**Page:**	

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS

Safety Results are summarised below:

Main safety results

		S 12911 (N = 22)	**Placebo (N = 21)**
Patients having reported			
at least one emergent adverse event	n (%)	21 (95.5)	20 (95.2)
at least one treatment-related emergent adverse event	n (%)	4 (18.2)	2 (9.5)
Patients having experienced			
at least one serious emergent adverse event (including death)	n (%)	4 (18.2)	7 (33.3)
at least one treatment-related serious emergent adverse event	n (%)	-	-
Patients withdrawn			
due to an adverse event	n (%)	4 (18.2)	-
Patients who died	n (%)	-	1 (4.8)

The frequency of patients who reported at least one **emergent adverse event** was similar in both treatment groups: 21 patients (95.5%) in the S 12911 group and 20 patients (95.2%) in the placebo group.

The most frequently affected system organ classes in the S 12911 group were:

- Musculoskeletal and connective tissue disorders: 16 patients in the S 12911 group and 14 patients in the placebo group.
- Infections and infestations: 7 patients and 8 patients, respectively.
- Gastrointestinal disorders: 7 patients and 8 patients, respectively.

The most frequent emergent adverse events reported in the S 12911 group were osteoarthritis (5 patients and 3 patients in the placebo group) and periarthritis (3 patients in each group). No relevant difference between the two groups was detected in the nature and frequency of emergent adverse events, except for skin and subcutaneous tissue disorders, more frequent in the S 12911 group (7 patients *versus* 2, respectively). Skin disorders reported in the S 12911 group were eczema (2 patients), acne, dermatitis allergic, nail disorder, generalised pruritus, psoriasis, rash, pruritic rash and chapped skin. These events occurred between 3 days (for rash) and about 11 months (for nail disorder) with an average time to onset around 6.5 months. None of these adverse events were serious. One adverse event (pruritic rash, with no associated signs) was considered related to the study treatment and led to study withdrawal. In the placebo group, two cases of skin disorders were reported: pruritus and rosacea.

Most emergent adverse events were graded as mild or moderate (99.1% of the events). **Severe emergent adverse events** occurred in 2 patients (1 patient in each group).

In both groups, the **treatment-related emergent adverse events** were sparse: 4 patients in the S 12911 group and 2 patients in the placebo group. Gastrointestinal disorders was the only system class affected more than once.

Premature study withdrawal due to adverse events affected 4 patients in the S 12911 group. Among them, one case of serious intestinal perforation and one case of osteoarthritis were not considered by the investigator to be related to the study treatment. One case of mouth ulceration and one case of mild rash pruritic were considered related to the study treatment.

Serious emergent adverse events were reported in 11 patients: 4 patients in the S 12911 group and 7 patients in the placebo group. These serious emergent adverse events were all considered to be unrelated to the study treatment, spanned 12 different system organ classes and did not display any meaningful trend.

One patient in the placebo group died during the study. He committed a complete suicide. This death was considered by the investigator to be unrelated to the study treatment but related to medical history.

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)*
Name of Finished Product: Protos®	**Volume:**	
Name of Active Ingredient: Strontium Ranelate (S 12911)	**Page:**	

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Laboratory tests

No relevant changes over time or differences between the two groups were detected for biochemical parameters except for CPK. The mean CPK value increased from baseline to end in the S 12911 group (mean change ± SD = 39.1 ± 82.8 IU/L) whereas it decreased in the placebo group (-44.9 ± 119.0 IU/L). However, there was no potentially clinically significant abnormal value in the S 12911 group (*i.e.* no values > 3 ULN (upper limit of the normal range)).

No clinically relevant change over time or differences between the two groups were detected for haematological parameters.

No clinically relevant changes over time or differences between the two groups were detected for vital signs.

CONCLUSION

This study aimed at assessing the effectiveness of a 2-year treatment with S 12911 on algofunctional symptoms of knee osteoarthritis, compared to placebo.

As only 43 patients were included in this study instead of 140 patients initially planned, the efficacy analysis was restricted to descriptive statistics. No conclusion could be drawn regarding the effect of S 12911 on the algofunctional symptoms in knee osteoarthritis.

S 12911 was well tolerated with no unexpected adverse event.

Date of the report: 14 April 2011