I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**Clinical Study Report Synopsis**
Study title	**The efficacy and safety of two doses of strontium ranelate (1g and 2g per day) versus placebo administered orally for 3 years (2 years initially planned then extended to 3 years by Amendment No. 11) in the treatment of knee osteoarthritis.** **A prospective multicentre, international, double-blind, placebo controlled study.**
Study drug	**S 12911**
Studied indication	**Osteoarthritis**
Development phase	**Phase III**
Protocol code	**CL3-12911-018**
Study initiation date	**28 April 2006**
Study completion date	**17 February 2011**
Main coordinator	███████████ **United Kingdom**
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50, rue Carnot** **92284 Suresnes Cedex - France** **Servier Canada Inc.** **235, Armand Frappier Blvd** **H7V 4A7 Laval (QC)- Canada** **Laboratorios Servier** **Avenida de los Madronos** **3328 043 Madrid - Spain** **Servier Research and Development** **Gallions, Whexham Springs - Framewood Road - Wexham** **Slough SL3 6RJ - United Kingdom**
Responsible medical officer	███████████████
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 20 March 2012**

~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Company: I.R.I.S. 50 rue Carnot 92284 – Suresnes Cedex - FRANCE	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: **Protelos® Osseor® (Europe)**	**Volume:**	
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Title of study: The efficacy and safety of two doses of strontium ranelate (1g and 2g per day) *versus* placebo administered orally for 3 years (2 years planned initially then extended to 3 years by Amendment No. 11) in the treatment of knee osteoarthritis. A prospective multicentre, international, double-blind, placebo-controlled study. Protocol No.: CL3-12911-018 Registered under EUDRACT number 2005-002494-75
International Coordinator: ███████████████████ United Kingdom.
Study centre*s*: Multicentre study with 98 centres in 18 countries having included at least 1 patient (1683 patients included): Australia (8 centres – 66 patients), Austria (4 centres – 57 patients), Belgium (5 centres – 115 patients), Canada (7 centres – 259 patients), Czech Republic (2 centres – 44 patients), Denmark (3 centres – 241 patients), Estonia (1 centre – 29 patients), France (20 centres – 73 patients), Germany (6 centres – 40 patients), Italy (7 centres – 103 patients), Lithuania (1 centre – 9 patients), Netherlands (3 centres – 16 patients), Poland (4 centres – 142 patients), Portugal (3 centres – 14 patients), Romania (1 centre – 27 patients), Russian Federation (7 centres – 94 patients), Spain (8 centres – 185 patients), United Kingdom (8 centres – 169 patients)
Publication (reference): NA

Studied period:
   Initiation date: 28 April 2006 (date of first selection)
   Completion date: 17 February 2011 (date of last completed visit)
	Phase of development of the study: III

Objectives: *Main objective:* - To demonstrate the superiority of strontium ranelate (SrRan) 1g and 2g per day *versus* placebo against articular cartilage damage progression, over two years extended to three years (Amendment No. 11), in men and women with knee osteoarthritis (OA), by measuring changes in cartilage joint. *Secondary objectives:* - To assess the effects of SrRan (1g and 2g per day) versus placebo on the other efficacy end-points and its safety, in addition to the effects on concomitant OA of the hip, of hands and on subchondral bone microarchitecture.
Methodology: International, multicentric, randomised using Interactive Voice Response System (IVRS) with stratification on centre and gender, double-blind, placebo-controlled study, with 3 parallel groups (SrRan 1g, SrRan 2g and placebo). 3 Committees were set-up: - The Executive Committee was in charge of the scientific and ethical aspects of the study and proposed amendments to the study protocol. This committee validated the final results and conclusions of the study. - The Steering Committee was in charge of practical and technical aspects of the study. - The Safety Committee composed of experts in the field of medical surveillance, was to inform and/or formulate recommendations in case of unexpected safety issues.

Number of patients:
   Planned: 960 included patients (320 patients in each group) amended to 2127 included patients (709 patients in each group) following Amendment No. 10 then 1680 patients (560 in each group) following Amendment No. 11.
   Included: 1683 patients (558 in the SrRan 1g group, 566 in the SrRan 2g group and 559 in the placebo group).

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Diagnosis and main criteria for inclusion:
Caucasian, ambulatory, men and women aged ≥ 50 years, with a primary knee OA of the medial femoro-tibial compartment diagnosed according to the clinical and radiological criteria of the American College of Rheumatology, a presence of Kellgren and Lawrence grading stages II or III on knee X-rays and a Joint Space Width (JSW) of at least 3 mm, modified by Amendment No. 9 to JSW between 2.5 and 5 mm (inclusive limits). A target knee was defined taking into account the Kellgren and Lawrence score, the anatomic compartment, and the VAS value at inclusion, and was then to be followed during the study.

Study drug:
Strontium Ranelate given orally as sachet of granules of 1g or 2g taken as a suspension once daily at bedtime.

Reference product:
Matching placebo sachet given orally as a suspension once daily at bedtime.

Duration of treatment:
From selection visit (W-2) to M0: period without study treatment
Active treatment period (M0-M36): 24 months extended to 36 months (Amendment No. 11) with two additional visits M30 and M36 and one additional phone call at M27

Criteria for evaluation:
Efficacy measurements

Primary efficacy endpoint:
Radiographic progression of knee osteoarthritis by assessment of the JSW at selection, M12, M24 and M36 visits (standardised assessment and centralised reading by PMO, Prevention des Maladies Osseuses, Lyon, France). The measurement of the mean change *versus* placebo in the minimal JSW of the medial femoro-tibial compartment was determined by X-ray.
A second independent central reading of knee X-ray using the same device and reading method was set up in LIEGE (Liege – Belgium).

Secondary efficacy endpoints:
- Radiological and radio-clinical progression of the knee osteoarthritis: number of failures, assessed by knee JSW progression (*i.e.* JSW loss ≥ 0.5 mm) and radio-clinical failure assessed by an index combining knee JSN and the WOMAC pain sub score (≤ 20%) at the last post baseline visit.
- Clinical assessments:
  • Algo-functional assessment of the target knee by the WOMAC index score (Western Ontario and McMaster Universities Osteoarthritis Index) every 6 months from M0 to M36.
  • Visual Analogic Score (VAS) for the target knee pain scale assessment at selection, M0, and every 6 months up to M36 with a recall period of 48 hours.
  • Target knee physical assessment at each visit.
  • Time to surgery for the target knee joint replacement amended to time to indication to surgery for target knee joint replacement (Amendment No. 10).
- E-diary filled in by the patient: knee pain flare frequency and intensity, and pain medication consumption through a once weekly phone call.
- SF36 Quality of Life Questionnaire self-administered questionnaire filled in at M0, and then every 6 months up to M36.
- Knee Magnetic Resonance Imaging (MRI), assessing the cartilage volume and other parameters (performed in a subset of patients) at M0, M12, M24 and M36 visits.
- Biochemical bone markers: serum Bone ALkaline Phosphatase (bALP) and C-terminal Telopeptides of type I collagen (CTX I) and cartilage markers: serum C Propeptide of type II procollagen (CPII) and urinary C-terminal Telopeptides of type II collagen (CTX II) and one marker of synovial metabolism Hyaluronic Acid (HA), at M0, M3, M6, M12, M24, M30, and M36.

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Criteria for evaluation (Cont'd):

- Hand radiological and clinical assessment:
  - Radiologic assessment of hand osteoarthritis at M0 and M36.
  - Clinical assessment of hand osteoarthritis.
  - Algo-functional assessment by AUStralian CANadian hand osteoarthritis Index (AUSCAN) and functional assessment by FIHOA index, in countries where these index were linguistically validated. As AUSCAN (self-administered) and FIHOA (doctor-administered) questionnaires relate similarly to the functional aspects of the hand OA, but are administered in a different way, both hand osteoarthritis indices were employed at M0, M12, M24 and M36 visits.
  - Clinical assessement by the investigator of pain in finger joints at M0, M12, M24, and M36 visits and of finger nodes at M0 and M36 visits only.
- Clinical assessment of both hips: pain assessed by the VAS score and physical examination at M0, M12, M24 and M36 visits.
- Exploratory assessments:
  - In addition to the central reading by PMO, the knee X-ray was evaluated by Synarc (San Fransisco, USA) using an exploratory method.
  - Radiological progression defined via an algorithm.
  - Subchondral bone architecture assessment at the knee level by non-invasive high resolution tomodensitometric method (CT-scan in selected centres) at M0 and M36.
  - Pharmacoeconomic assessment (need for: physiotherapy, nursing care sessions, paramedical sessions, additional medical imaging procedures or physician visits, hospitalisation for knee inflammation, total knee replacement, knee arthroscopy, rehabilitation unit admission and water cures, drugs consumption) at M3 visit (Amendment No. 8), M6, M12, M18, M24, M30 and M36.

Safety measurements:

- Adverse events reported at each visit.
- Vital signs (weight, height, systolic and diastolic blood pressure, heart rate) at each visit.
- Laboratory safety parameters: biochemistry parameters [total alkaline phosphatase, ASAT, ALAT, GGT, blood and urinary creatinine, phosphorus, blood and urinary calcium, sodium, potassium, chloride, albumin, C-reactive protein, CPK (and isoenzymes if CPK above the upper limit of the reference range)] and haematology parameters (blood cell count, haemoglobin, haematocrit, MCV) at selection, M3, M6, M12, M18, M24, M30 and M36 except for sodium, potassium, chloride assessed only at selection, M12, M24 and M36 visits.
- Haemostasis parameters (prothrombin time, activated partial thromboplastine time, prothrombin activation peptide (F1 + F2 fragments), fibrinogen, antithrombin III, protein C, protein S, factor VIII, homocystein (and folic acid and vitamin B12 if homocystein above the upper limit of the reference range), antiphospholipid antibodies assessed at M0, M6, M12, M24 and M36.

Pharmacokinetic measurements

To assess the pharmacokinetics (PK) of strontium in patients with knee osteoarthrisis, serum samples were collected in all patients in the morning of M0, M3, M6 and every 6 months up to M36. Additionally, at M6 and M18, in a subgroup, the patients were asked to take their daily treatment in the morning during the visit, after the first blood collection. In these patients, an additional blood sample was collected between 1h30 and 4h after the morning study treatment intake. At M30, in the same subgroup, an additional blood sample was collected between 1h30 and 4h after the first sampling in the morning but without taking any medication before.

Serum concentrations of strontium were assessed by high frequency inductively coupled plasma atomic emission spectrometry (ICP-AES).

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Statistical methods:

Study outcome: descriptive statistics were provided.

Efficacy analyses were primarily performed in the Full Analysis Set (FAS) defined as all randomised patients who took at least one dose of the study treatment and who had one assessable baseline and at least one assessable post-baseline evaluation of the JSW as defined by the central reader located in Lyon (PMO). The analyses were also performed in the PPS, defined as all patients of the FAS without relevant deviations which could affect the evaluation of the JSW.

Primary criterion
Main Analysis
The JSW (from PMO reading) was expressed as the change from baseline to last post-baseline value. Each SrRan group was compared to the placebo group in the FAS using a general linear model (with Dunnett's multiple comparison procedure, placebo being the reference group) with baseline JSW, centre and gender as covariates. Estimates (E) of the difference between adjusted group means and Standard Error (SE) of the estimate were provided with its 95% CI and the associated p-value. The main analysis was also performed on the Per Protocol Set (PPS).

Sensitivity analyses
The SrRan groups were compared to the placebo group on the evolution of JSW change over time using different statistical models (mixed model for repeated measurements, multiple imputation, pattern mixture model). A sensitivity analysis was also performed in the Randomised Set after substitution of missing values by the mean level in the placebo group.
JSW results from LIEGE reading
SrRan 1g and SrRan 2g treatment groups were compared to placebo on the change from baseline to each visit, using a general linear model with baseline, gender and centre as covariates.

Secondary Analyses
The main analysis was performed in a subgroup of patients from the FAS with a Kellgren-Lawrence stage on the target knee equal to III (and II, complementary analysis) at inclusion. The main analysis was also applied to the change and the relative change in JSW from baseline to each visit and to last post-baseline value.

Secondary criteria
The SrRan 1g and SrRan 2g groups were compared to the placebo group using the following statistics:
- Radiological and radio-clinical progression of the knee osteoarthritis: comparisons were performed using a Chi² test.
- Clinical assessments
  • WOMAC scores for the target knee: comparisons were performed on the WOMAC scores absolute and relative changes and the treatment effect was averaged over time using a mixed model for repeated measurements gender and centre as covariates, and for absolute change with baseline value. For WOMAC pain subscore responders, a Chi² test was also used.
  • VAS knee pain: similar analyses as for the WOMAC global score were performed.
  • Knee physical assessment: comparisons were performed on the number of swelling / warmth / effusion reported during the study using a general linear model with gender and centre as covariates.
  • Indication to knee surgery for target knee joint replacement: descriptive statistics were provided.
  • E-diary: descriptive statistics were provided at each 6-month period until M36 on the number of reliable calls, the E-diary compliance, the feeling of pain, the intensity of pain, the mean numbers of days with pain per week and the pain medication consumption (duration and mean dose/week).
  • Quality of life: SF36 questionnaire: similar analyses as for the hand osteoarthritis score were performed for each dimension and global score.

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Statistical methods (Cond't):
Efficacy analyses (Cont'd)
Secondary criteria (Cont'd)

- Knee MRI parameters: comparisons were performed on the absolute and relative change from baseline to each visit, using a general linear model with baseline (only for absolute change), gender and centre as covariates.
- Biochemical cartilage and bone markers: similar analyses as for the MRI parameters were performed.
- Hand radiological and clinical assessment:
  - Hand osteoarthritis X-ray evaluation: comparisons were performed on the absolute and relative change from baseline to last post-baseline value, using a general linear model with baseline (only for absolute change), gender and centre as covariates.
  - Algo-functional assessment of hand: SrRan 1g and SrRan 2g treatment groups were compared to placebo on the change (relative change) from baseline to last post-baseline value of AUSCAN scores and FIHOA score, using a general linear model with baseline (only for absolute change), gender and centre as covariates.
- Hip clinical assessment: descriptive statistics were provided for each treatment group for the functional assessment, the VAS, and the occurrence of hip prosthesis implantation.
- Exploratory assessments:
  - JSW from Synarc reading: comparisons were performed on the change from baseline to each visit, using a general linear model with baseline, gender and centre as covariates.
  - Radiological progression defined via an algorithm: comparisons were performed using a Chi² test.
  - Knee subchondral bone architecture (CT-scan): change from baseline to the last post-baseline value on treatment were provided for each treatment group.
  - Pharmacoeconomic parameters: descriptive statistics were provided for each treatment group.

Safety analysis:
Adverse events, laboratory parameters and vital signs were analysed through descriptive statistics.

Pharmacokinetic analysis
Descriptive statitistics on strontium concentrations were calculated at each nominal sampling time per group. Strontium concentrations collected in the present study were pooled all together to build a population PK model in order to analyse these sparse PK data, to explain the sources of variability through a covariate analysis and to derive seconday PK parameters, *i.e.* $AUC_{24\ ss}$ and $C_{min\ ss}$. The method used for this population PK analysis is described in a separate data analysis plan.

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SUMMARY - CONCLUSIONS
STUDY POPULATION AND OUTCOME

Disposition of patients

Status	SrRan 1g n (%)	SrRan 2g n (%)	Placebo n (%)	All n (%)
Included	**558 (100.0)**	**566 (100.0)**	**559 (100.0)**	**1683 (100.0)**
in compliance with the protocol	520 (93.2)	516 (91.2)	514 (91.9)	1550 (92.1)
with a protocol deviation at inclusion	38 (6.8)	50 (8.8)	45 (8.1)	133 (7.9)
Lost to follow-up	**1 (0.2)**	**2 (0.4)**	**3 (0.5)**	**6 (0.4)**
Withdrawn from the study due to	**245 (43.9)**	**238 (42.0)**	**220 (39.4)**	**703 (41.8)**
adverse event	75 (13.4)	84 (14.8)	58 (10.4)	217 (12.9)
lack of efficacy	10 (1.8)	9 (1.6)	9 (1.6)	28 (1.7)
non-medical reason	151 (27.1)	135 (23.9)	147 (26.3)	433 (25.7)
protocol deviation	9 (1.6)	10 (1.8)	6 (1.1)	25 (1.5)
Completed	**312 (55.9)**	**326 (57.6)**	**336 (60.1)**	**974 (57.9)**
in compliance with the protocol	261 (46.8)	274 (48.4)	284 (50.8)	819 (48.7)
with a protocol deviation after inclusion	51 (9.1)	52 (9.2)	52 (9.3)	155 (9.2)
under study treatment	286 (91.7*)	301 (92.3*)	312 (92.9*)	899 (92.3*)
Analysis Set				
Full Analysis Set (FAS)	445 (79.7)	454 (80.2)	472 (84.4)	1371 (81.5)
Per Protocol Set (PPS)	277 (49.6)	290 (51.2)	298 (53.3)	865 (51.4)
Safety Set (SS)	548 (98.2)	564 (99.6)	556 (99.5)	1668 (99.1)

n Number of patients by group in a given analysis set.
% calculated as percentage of randomised patients, except * % of completed patients.

A total of 1683 patients were included and randomly assigned to one of the 3 treatment groups, with a well balanced distribution: 558 patients in the SrRan 1g group, 566 in the SrRan 2g group and 559 in the placebo group. Of them, 703 patients (41.8%) withdrew from the study, mainly due to non-medical reasons (433 patients, 25.7%). Among these 433 patients, 45 patients, 10.4% of the withdrawn patients withdrew due to: no patient's improvement (35 patients, 8.1%), worsening of OA (9 patients, 2.1%) or planned knee replacement (1 patient, 0.2%) (complementary analysis).

Other reasons were: adverse events (217 patients, 12.9%), with a slightly higher rate in the active treatment groups (13.4% in the SrRan 1g group, 14.8% in the SrRan 2g group) than in the placebo group (10.4%), lack of efficacy (28 patients, 1.7%), and protocol deviations (25 patients, 1.5%). Six patients were lost-to-follow-up: 1 patient in the SrRan 1g group, 2 patients in the SrRan 2g group and 3 patients in the placebo group.

Overall, 784 patients (46.6% of the randomised patients) prematurely discontinued the study treatment, mainly due to non-medical reasons (25.1%) and adverse events (18.1%).

Finally, 974 patients (57.9% of the Randomised patients) completed the study of whom 899 patients (92.3% of the completed patients) completed the study under treatment while the other 75 (7.7%) had prematurely discontinued the study treatment.

Demographic and other baseline characteristics in the Randomised Set fulfilled the inclusion criteria of the study protocol, with no relevant between-group differences.

Patients were on average 62.9 ± 7.5 years old (range: 49-88 years) and 40.6% were 65 years or older, with higher rate in the SR 2g group than in the other groups: 38.2% in the SR 1g group, 44.7% in the SR 2g group, and 38.8% in the placebo group. The majority of patients were women (70.4%). Mean BMI was 29.9 ± 5.0 kg/m² and 44.2% of the patients were obese (BMI ≥ 30 kg/m²). About half of them (46.5%) reported alcohol consumption habit and 10.9% were smokers.

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SUMMARY - CONCLUSIONS (Cont'd)
STUDY POPULATION AND OUTCOME (Cont'd)

Patients were suffering from knee OA for 6.4 years in average (median = 4.4 years). Mean baseline JSW of the target knee was 3.50 ± 0.84 mm with a Kellgren and Lawrence rated stage II for a majority of patients (61.7%) and stage III for 38.1% of them. The mean baseline WOMAC global score (/300 mm) was 132.4 ± 62.4 mm with no between-group difference.

Main baseline demographic characteristics and characteristics of knee osteoarthritis in the Randomised Set (N = 1683)

		SrRan 1g (N = 558)	SrRan 2g (N = 566)	Placebo (N = 559)	ALL (N = 1683)
Age (years)	Mean ± SD	62.4 ± 7.4	63.5 ± 7.5	62.8 ± 7.5	62.9 ± 7.5
Men	n (%)	164 (29.4)	167 (29.5)	167 (29.9)	498 (29.6)
Women	n (%)	394 (70.6)	399 (70.5)	392 (70.1)	1185 (70.4)
BMI (kg/m²)	Mean ± SD	30.1 ± 5.1	29.8 ± 4.8	29.8 ± 5.1	29.9 ± 5.0
Kellgren and Lawrence stage Stage II	n (%)	341 (61.2)	347 (61.3)	350 (62.6)	1038 (61.7)
Kellgren and Lawrence stage Stage III	n (%)	214 (38.4)	218 (38.5)	209 (37.4)	641 (38.1)
Knee JSW reading by PMO (mm)	Mean ± SD	3.45 ± 0.87	3.54 ± 0.8	3.51 ± 0.83	3.50 ± 0.84
WOMAC global score /300 mm	Mean ± SD	132.0 ± 62.0	136.4 ± 62.5	129.0 ± 62.5	132.4 ± 62.4
Pain subscore/100 mm	Mean ± SD	42.7 ± 21.3	44.5 ± 21.8	42.2 ± 21.6	43.2 ± 21.6
Stiffness subscore/100 mm	Mean ± SD	46.8 ± 24.9	48.3 ± 25.0	45.5 ± 25.2	46.9 ± 25.0
Physical function subscore/100 mm	Mean ± SD	42.5 ± 21.9	43.7 ± 22.5	41.0 ± 22.4	42.4 ± 22.3
Knee VAS pain /100 mm	Mean ± SD	52.6 ± 22.5	55.6 ± 21.9	53.7 ± 22.4	54.0 ± 22.3

Baseline selection visit
n number of patients
% calculated as percentage of randomised patients

At inclusion, 72.5% of the patients evaluable for the Kellgren and Lawrence (KL) score, had a hand OA (*i.e.* had at least 2 finger joints scored at a KL grade 2 or more at baseline) and 30% of the patients had a family history of hand OA; 10.6% of the patients suffered from hip OA (based on clinical assessment, no systematic radiography was performed).

More than one third of the patients (37.9%) were receiving a previous treatment for OA at inclusion, with a slightly lower frequency in the SrRan 1g group than in the other groups: 33.9% in the SrRan 1g group, 40.3% in the SrRan 2g group, and 39.5% in the placebo group. These treatments were mainly antiinflammatory and antirheumatic products (29.8%), mostly glucosamine (11.4%), and corticosteroids for systemic use (7.0%).

Most patients (99.3%) reported a medical history in addition to OA, mostly vascular disorders (55.9%) including hypertension (45.5%), and metabolism and nutrition disorders (48.1%), including hypercholesterolaemia (21.9%). Consistently with their medical history, main concomitant treatments taken by the patients at inclusion consisted of agents acting on the renin-angiotensin system (29.6% of the patients), and lipid modifying agents (25.2%).

Patients in the three treatment groups had similar demographic and baseline characteristics.

In the FAS, demographic and other baseline characteristics were close to those of the Randomised Set.
The global compliance was good: 86.5% of the patients had a compliance within the [85-130 %[range, and the mean global compliance was 93.3 ± 9.3%. In the FAS, the mean treatment duration was 29.8 ± 10.5 months, *i.e.* 2.5 years, with a median of 35.7 months (*i.e.* about 3.0 years).

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**SUMMARY - CONCLUSIONS (Cont'd)**

EFFICACY RESULTS

Primary efficacy criterion: minimum Joint Space Width (JSW) of the knee

- **Main analysis: change from baseline to last post-baseline value**

The mean JSW decreased from baseline to the last post-baseline value in all groups, less markedly in both SrRan treatment groups than in the placebo group. The mean changes were, in the FAS:

- SrRan 1g group: mean $\pm$ SD = -0.23 $\pm$ 0.56 mm   (median = -0.15 mm).
- SrRan 2g group: mean $\pm$ SD = -0.27 $\pm$ 0.63 mm   (median = -0.17 mm).
- Placebo group: mean $\pm$ SD = -0.37 $\pm$ 0.59 mm   (median = -0.30 mm).

The statistical analysis showed that the JSW loss was significantly reduced in both SrRan groups compared to the placebo group:

- SrRan 1g group: E (SE) = 0.14 (0.04) mm, 95% CI = [0.05 ; 0.23], p < 0.001.
- SrRan 2g group: E (SE) = 0.10 (0.04) mm, 95% CI = [0.02 ; 0.19], p = 0.018.

Knee JSW (mm) - Change from baseline to End in the FAS (N = 1371)

		SrRan 1g (N = 445)	SrRan 2g (N = 454)	Placebo (N = 472)
Baseline	n	445	454	472
	Mean $\pm$ SD	3.45 $\pm$ 0.86	3.53 $\pm$ 0.80	3.51 $\pm$ 0.82
	Median	3.48	3.51	3.48
	Min ; Max	0.68 ; 6.00	1.88 ; 6.58	0.65 ; 5.80
END (last post-baseline value)	n	445	454	472
	Mean $\pm$ SD	3.23 $\pm$ 1.06	3.25 $\pm$ 1.03	3.15 $\pm$ 1.00
	Median	3.27	3.22	3.13
	Min ; Max	0.613 ; 5.91	0.55 ; 6.48	0.38 ; 5.54
Change from baseline to END	n	445	454	472
	Mean $\pm$ SD	-0.23 $\pm$ 0.56	-0.27 $\pm$ 0.63	-0.37 $\pm$ 0.59
	Median	-0.15	-0.17	-0.30
	Min ; Max	-2.89 ; 1.67	-4.27 ; 1.6	-3.34 ; 1.59
Statistical analysis	E (SE) [1]	0.14 (0.04)	0.10 (0.04)	-
	95% CI [2]	[0.05 ; 0.23]	[0.02 ; 0.19]	-
	p-value [3]	**< 0.001**	**0.018**	-

n number of assessable patients
(1) Estimate (Standard error) of the difference between treatment group means SrRan 1g or 2g minus placebo adjusted on baseline, gender, and centre; (2) Dunnetts 95% Confidence interval of the estimate; (3) Dunnetts adjusted p-value (general linear model with baseline as covariate and gender and centre as fixed factors)

There was no statistically significant difference between the two SrRan groups (p = 0.38, complementary analysis).

Sensitivity analyses (mixed model for repeated measurements, multiple imputation, pattern mixture model and analyses on the Randomised Set after substitution of missing JSW loss values in SrRan and placebo groups by the mean levels in the placebo group) confirmed the results of the main analysis.

Results were also confirmed in the PPS with slightly higher estimates of the between-group differences (SrRan 1 or 2g *versus* placebo) than in the FAS:

- SrRan 1g group: E (SE) = 0.16 (0.05) mm, 95% CI = [0.05 ; 0.27], p = 0.003.
- SrRan 2g group: E (SE) = 0.13 (0.05) mm, 95% CI = [0.02 ; 0.24], p = 0.015.

The JSW **results from LIEGE reading** (second independent central reader) confirmed those from PMO central reading.

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SUMMARY - CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

- **Secondary analysis**

Knee JSW: change and relative change from baseline to each visit
The decrease in the mean JSW was significantly lower in the SrRan treatment groups in comparison with the placebo group at all visits (M12, M24, M36).

JSW (mm) - Change from baseline to each visit in the FAS (N = 1371)
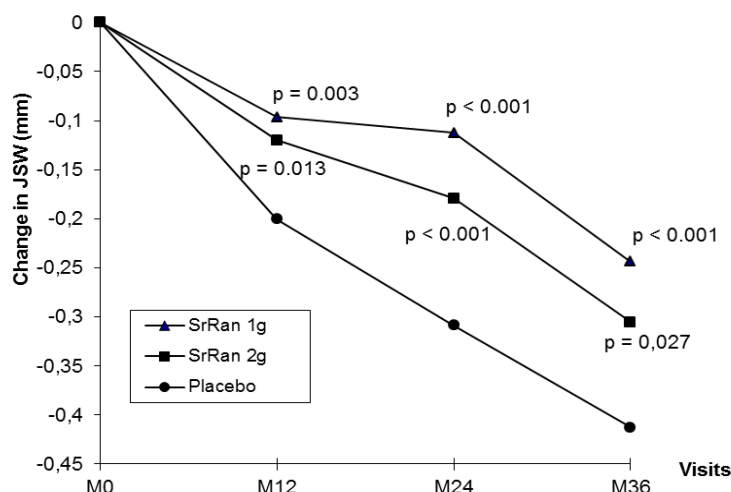
Statistical analysis SrRan groups versus placebo group Dunnetts adjusted p-value (general linear model with baseline as covariate and gender and centre as fixed factor)

The results expressed as relative changes confirmed those expressed as changes.

Subgroup analysis according to Kellgren-Lawrence stage at inclusion
Regardless of the baseline Kellgren-Lawrence stage, the JSW loss was lower in SrRan 1g or 2g treated patients compared to patients on placebo. The differences *versus* placebo were higher in patients with Kellgren-Lawrence stage II at inclusion *i.e.* the less severe patients:

- **Kellgren-Lawrence stage II at inclusion** (complementary analysis)**:** JSW loss = -0.18 ± 0.54 mm in the SrRan 1g group (N = 268), -0.20 ± 0.59 mm in the SrRan 2g group (N = 274), and -0.33 ± 0.57 mm in the placebo group (N = 299).
  Statistical analysis *versus* placebo:
  - SrRan 1g group: E (SE) = 0.16 (0.05) mm, 95% CI = [0.05 ; 0.26], p = 0.003.
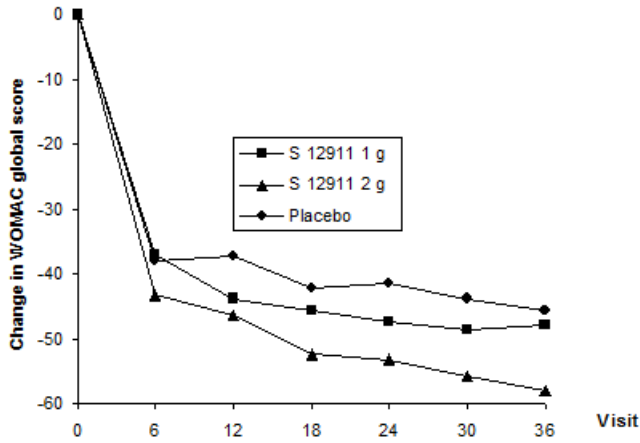 - SrRan 2g group: E (SE) = 0.14 (0.05) mm, 95% CI = [0.03 ; 0.25], p = 0.007.
- **Kellgren-Lawrence stage III at inclusion:** JSW loss = -0.31 ± 0.59 mm in the SrRan 1g group (N = 174), -0.39 ± 0.68 mm in the SrRan 2g group (N = 179), and -0.44 ± 0.63 mm in the placebo group (N = 173).
  Statistical analysis *versus* placebo:
  - SrRan 1g group: E (SE) = 0.10 (0.07) mm, 95% CI = [-0.05 ; 0.25], p = 0.241.
  - SrRan 2g group: E (SE) = 0.04 (0.07) mm, 95% CI = [-0.12 ; 0.18], p = 0.825.
  The lack of statistical significance could be explained by the limited number of patients in this subgroup.

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SUMMARY - CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)
Secondary criteria
- **Radiological and radio-clinical progression of the knee osteoarthritis**
Radiological failures, defined as a knee JSW loss $\geq$ 0.5 mm on the last post-baseline visit, were significantly less frequent in the SrRan treatment groups than in the placebo group:
- 22.3% in the SrRan 1g group, $p < 0.001$ *versus* placebo.
- 25.6% in the SrRan 2g group, $p = 0.012$ *versus* placebo.
- 33.1% in the placebo group.

The relative risk reduction (RRR) compared to placebo was 32.7% in the SrRan 1g group with a number of patients needed to be treated to prevent one case (NNT) of 10 patients, and 22.7% in the SrRan 2g group with a NNT of 14 patients over the study period (complementary analysis).

The radio-clinical failures (defined as a knee JSW loss $\geq$ 0.5 mm associated to a clinical change $\leq$ 20% on the pain subscale of the WOMAC score at the last post-baseline visit) were significantly less frequent in the SrRan treatment groups than in the placebo group:
- 7.7% in the SrRan 1g group, $p = 0.049$ *versus* placebo.
- 6.5% in the SrRan 2g group, $p = 0.008$ *versus* placebo.
- 11.6% in the placebo group.

The RRR was 34.0% in the SrRan 1g group with a NNT of 26 patients, and 44.1% in the SrRan 2g group with a NNT of 20 patients over the study period (complementary analysis).

- **WOMAC score for the target knee**
The mean **WOMAC global score** decreased in all treatment groups during the study indicating an improvement of the patients. The evolution of the change in WOMAC global score from baseline to each post-baseline visit is illustrated in the figure below.
The improvement was more marked in the SrRan 2g group than in the placebo group: the change from baseline to the last post-baseline evaluation was in average more than 10 points higher in the SrRan 2g group than in the placebo group (-51.9 $\pm$ 66.1mm *versus* -40.7 $\pm$ 69.1 mm, respectively).
The planned statistical approach considering all post-baseline values (mixed model for repeated measurements with baseline as covariate and gender and centre as fixed factors) showed a statistical trend in favour of the 2g dose:
- SrRan 1g group: E (SE) = -1.8 (3.1) mm, $p = 0.563$.
- SrRan 2g group: E (SE) = -5.7 (3.1) mm, $p = 0.071$.

When using a similar statistical approach as for the primary criterion JSW, *i.e.* when considering the last post baseline evaluation (Last Observation Carried Forward -LOCF- approach, complementary analysis), the improvement was statistically significant in the SrRan 2g group while no statistically significant difference was found between the SrRan 1g group and the placebo group:
- SrRan 1g group: E (SE) = -1.3 (4.0) mm, $p = 0.749$.
- SrRan 2g group: E (SE) = -8.0 (4.0) mm, $p = 0.045$.

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SUMMARY - CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

WOMAC global score (mm) - Mean changes from baseline to each visit in the FAS (N = 1371)

- **WOMAC subscores**
The treatment with SrRan 2g resulted in an improvement in all three subscores, compared to placebo or SrRan 1g treatments. The improvement in mean pain subscore was statistically significant in the SrRan 2g group compared to placebo (change from baseline to last value: -19.1 ± 23.7 mm in the SrRan 2g *versus* -14.7 ± 23.5 mm in the placebo group; $p = 0.028$, complementary analysis).
The rate of patients having an improvement of 20% in the average pain WOMAC subscore at last post-baseline evaluation (complementary analysis) was significantly increased in SrRan 2g treated patients (72.0%, $p = 0.010$ *versus* placebo) while this rate was similar in the SrRan 1g group and in the placebo group (64.5% and 64.0%, respectively).
The rate of responders 50 was also higher in the SrRan 2g group than in the placebo group (50.7% *versus* 44.8%, respectively), with a borderline significant p value (0.078). No statistically significant effect of SrRan 2g was found in the rate of responders 70.

- **VAS for the knee pain scale**
The VAS knee pain markedly decreased over time in all treatment groups, including in placebo-treated patients, indicating an improvement of the patients. At M36, the improvement was slightly more marked in the SrRan 2g group (-31.9 ± 27.3 mm) than in the SrRan 1g group and the placebo group (-26.0 ± 27.8 mm and -28.0 ± 28.5 mm, respectively) in the FAS, but there was no statistically significant difference between SrRan groups and placebo group.

- **Knee physical assessment**
Few patients were affected by symptoms of swelling (16.6% of the patients), warmth (3.4%) or effusion (12.0%) at their entry in the study.
This rate remained roughly stable over the study, with no relevant differences between the SrRan treatment groups (1 or 2g) and the placebo group.

- **Indication to knee surgery**
The indication for a knee surgery during the study (defined as a knee prosthesis implanted or a withdrawal for planned knee replacement) was reported in 8 patients: 3 in the SrRan 1g group, 3 in the SrRan 2g group and 2 in the placebo group.

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SUMMARY - CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

- **E-diary: pain and medications for pain**

Over the M0-M36 period, a tendency to a lower frequency of patients receiving at least one pain medication for the selected knee was observed in the SrRan 2g group compared to the placebo group: 88.8% in the SrRan 1g group, 86.0% in the SrRan 2g group, *versus* 90.4% in the placebo group. The other information collected by the patients in the e-diary, relative to pain (intensity, duration, number of days with pain) and the consumption of pain medication (number of drugs, pharmacological class) were similar in all treatment groups over the M0-M36 period.

- **Quality of life questionnaire (SF36)**

In all treatment groups, Physical Component Summary (PCS) and Mental Component Summary (MCS) scores remained stable or slightly increased from baseline to End. When analysing independently each dimension, between-group differences in the relative changes from baseline to End were of small amplitude, but generally in favour of the SrRan groups 1g or/and 2g. In particular, the item "physical role" increased by $16.4 \pm 57.8\%$ in the SrRan 1g group, $25.3 \pm 107.1\%$ in the SrRan 2g group and $15.6 \pm 76.7\%$, in the placebo group and "general health": $10.3 \pm 56.1\%$, $11.8 \pm 69.7\%$ and $7.5 \pm 40.4\%$, respectively.

- **Biochemical cartilage and bone markers**

Cartilage and synovitis markers

The levels of urinary CTX II (marker of cartilage degradation) decreased at M3 in the SrRan groups (-0.045 ± 0.220 μg/mmol creatinine in the SrRan 1g group, -0.064 ± 0.297 μg/mmol in the SrRan 2g group, -0.001 ± 0.238 μg/mmol in the placebo group) and remained lower than the baseline value at the following visits, whereas the levels were more fluctuating around baseline in the placebo group. The differences *versus* placebo were significant in both SrRan groups at M3 ($p = 0.018$ in the SrRan 1g group and $p < 0.001$ in the SrRan 2g group) and at M24 ($p = 0.007$ and $p = 0.036$, respectively), suggesting a lower level of cartilage degradation in SrRan-treated patients than in placebo-treated patients.

No significant effect of SrRan treatment was detected in exploratory cartilage markers serum hyaluronic acid (marker of synovial inflammation) and serum CPII (marker of cartilage synthesis).

Bone markers

Compared to placebo, mean serum b-ALP increased in both SrRan treatment groups compared to placebo. The difference *versus* placebo was significant in both SrRan groups at M3, and at all the subsequent visits except M24 in the SrRan 2g group. Serum CTX I decreased in both SrRan treatment groups compared to placebo. The differences *versus* placebo were significant in both SrRan groups all the visits until M24. Mean changes from baseline to M36 were for bALP (ng/mL): 0.06 ± 4.01 in the SrRan 1g group, 0.58 ± 4.37 in the SrRan 2g group, and -0.19 ± 4.20 in the placebo group, and for CTX I (ng/mL): 0.01 ± 0.19, 0.01 ± 0.21, and 0.02 ± 0.22, respectively. These results are in agreement with the dual mechanism of action of SrRan, as they suggest an increase in bone formation and a decrease in bone resorption with SrRan.

- **Knee MRI parameters**

The increase from baseline to the last post-baseline value in the global score for bone marrow lesion was slightly lower in the two treated groups (relative changes: $6.8 \pm 91.8\%$ in the SrRan 1g group, $19.0 \pm 110.6\%$ in the SrRan 2g group) than in the placebo group ($35.4 \pm 114.4\%$), although the between-group difference was not statistically significant. A slightly higher number of patients had an improvement (complementary analysis) in bone marrow lesion in both treated groups compared to placebo: 20 patients (17.9%), 18 patients (17.1%) and 14 patients (12.7%) in the SrRan 1g, 2g and placebo group respectively. In parallel, the number of patients with a worsening was numerically lower in the SR 2g group: 27 patients (25.7%) in the SrRan 2g group compared to 33 patients (29.5%) and 31 patients (28.2%) in the SrRan 1g group and placebo group respectively. When considering each compartment (medial and lateral) separately, the absolute change in the medial bone marrow lesion score between the baseline and last post-baseline values was significantly lower in the SrRan 2g group compared to the placebo group ($p = 0.034$, complementary analysis).

No clinically relevant change over time, nor between-group differences were detected regarding other MRI parameters.

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SUMMARY - CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

- **Hand radiological and clinical assessment**

At baseline, of the 1202 patients having a hand X-ray evaluation, 878 were evaluable for the KL score, with a mean value of 21.3 ± 13.3, and no between-group difference.

- **The X-ray evaluation** of hand OA performed with the 3 radiological scores (Kellgren-Lawrence, Kallman and Verbruggen-Veys scores) showed a slight progression of hand OA, with no statistically significant difference between the SrRan treatment groups and the placebo group.
- **The algo-functional assessment of the hand** showed an improvement of the patients during the study. The AUSCAN global score and subscores tended to improve in the SrRan treatment groups, with a more marked effect with the 2g dose. The rate of responders 20% were 49.6% in the SrRan 1g group, 53.8% in the SrRan 2g group, and 45.6% in the placebo group. The difference *versus* placebo was significant in the SrRan 2g group: E (SE) = 8.21 (4.12), 95% CI = [0.13 ; 16.30]. The FIHOA score slightly decreased in all groups during the study, showing an improvement of the physical function of the hands of the patients. No between-group difference was detected.

- **Hip clinical assessment**

Among the patients having hip OA at baseline (11.7% of the patients in the SrRan 1g group, 10.8% in the SrRan 2g group, and 11.9% in the placebo group), the VAS showed a marked decrease in the hip pain from baseline to the last value in the SrRan treatment groups in comparison with the placebo group: -13.4 ± 31.4 mm in the SrRan 1g group, -21.8 ± 24.9 mm in the SrRan 2g group, and -5.0 ± 33.5 mm in the placebo group, when considering the most painful hip at baseline (complementary analysis), although no statistical difference between SrRan groups and placebo group was reached (p = 0.19 and p = 0.12, respectively).

- **Exploratory assessments**

No relevant treatment effect was observed for exploratory assessments: knee sunchondral bone architecture (CT-scan), pharmaco-economic parameters, JSW results obtained from Synarc. Results of the radiological progression, according to an exploratory algorithm, were consistent with those obtained without algorithm.
Pharmaco-economic parameters assessed during the study showed that fewer patients needed physiotherapy, additional imaging or physician visits or other paramedical sessions at the end of the study than at their entry, with no relevant difference between-group difference.

- **Pharmacokinetic/Pharmacodynamic results**

Using a population modelling approach, the pharmacokinetics (PK) of strontium was described by a two-compartment model with first-order absorption and elimination. In accordance with previous knowledge on strontium PK, the bioavailability ▮▮▮▮▮▮▮▮▮ at the 2g dose as compared to the 1g dose. Strontium apparent clearance ▮▮▮▮▮▮▮ was associated with ▮▮ and ▮▮ of inter- and intra-individual variability, respectively and was influenced by several covariates (*e.g.* creatinine clearance, calcium, phosphoremia, BMI and, to a negligeable extent, albuminemia), without being affected by age or gender. Creatinine clearance was the most significant covariate. Overall, the significant covariates, all together, explained only ▮▮ of the inter-individual variability observed on the apparent clearance of strontium. Steady-state serum exposure to strontium (*i.e.* mean ▮▮▮▮▮ ▮ ▮) was ▮▮ ▮▮▮▮▮ and ▮▮ ▮▮▮▮ and trough serum concentrations of strontium (i.e. mean $C_{min,ss} \pm SD$) were ▮▮ ▮▮▮▮ and ▮▮ ▮▮▮▮ for SrRan doses of 1g and 2g, respectively.

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SUMMARY - CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

A graphical exploratory data analysis investigating relationships between strontium serum exposure and cardilage degradation marker u-CTX II on one hand and u-CTX II and JSN on the other hand, revealed significant relationships between:

- Strontium $AUC_{24,ss}$ and u-CTX II expressed as percent change from baseline ($p < 0.01$).
- U-CTX II (expressed as percent change from baseline) and JSN improvement ($p < 0.01$).

Furthermore, a trend was found between the WOMAC score or the WOMAC pain subscore and either strontium exposure or SrRan dose. To consolidate PK/PD exploratory data analysis findings, population models were developed to describe on one hand, the relationship between strontium exposure and u-CTXII, and on the other hand, between strontium exposure and WOMAC score and WOMAC pain sub-score. Results showed a statistically significant relationship between the strontium exposure and the u-CTXII, confirming the structure-modifying effects of strontium ranelate. Regarding WOMAC score pain sub-score, the existence of statistically significant linear relationships between strontium exposure and WOMAC score and WOMAC pain sub-score in OA patients was demonstrated.

SAFETY RESULTS

Summary of safety results

		SrRan 1g (N = 548)	SrRan 2g (N = 564)	Placebo (N = 556)
Patients having reported				
at least one emergent adverse event	n (%)	470 (85.8)	496 (87.9)	481 (86.5)
at least one treatment-related emergent adverse event	n (%)	156 (28.5)	183 (32.4)	148 (26.6)
at least one serious emergent adverse event (including death)	n (%)	93 (17.0)	93 (16.5)	97 (17.4)
at least one treatment-related serious adverse event	n (%)	7 (1.3)	8 (1.4)	4 (0.7)
an emergent adverse event leading to treatment stopped	n (%)	91 (16.6)	117 (20.7)	90 (16.2)
at least one emergent VTE	n (%)	5 (0.9)	3 (0.5)	1 (0.2)
Patients who died during the study*	n (%)	3 (0.5)	2 (0.4)	1 (0.2)

*% calculated as percentage of the patients of the safety Set except * calculated as percentage of patients in the Randomised Set*
VTE Venous thromboembolic event   deep vein thrombosis and/ or pulmonary embolism

Adverse events
The overall frequency of patients who reported at least one emergent adverse event was close in the three treatment groups: 470 patients (85.8% of the patients) in the SrRan 1g group, 496 patients (87.9%) in the SrRan 2g group and 481 patients (86.5%) in the placebo group.
The most frequently affected system organ classes were musculoskeletal and connective tissue disorders (44.2% of the patients in the SrRan 1g group and 46.8% in each of the other groups), infections and infestations (38.3% in the SrRan 1g group, 37.4% in the SrRan 2g group and 39.2% in the placebo group) and gastrointestinal disorders (29.7%, 29.1% and 29.9%, respectively). Most system organ classes were reported at comparable incidence in the three groups, except for skin and subcutaneous tissue disorders more frequently reported in the SrRan 2g group than in the placebo group group (16.3% *versus* 12.2%, respectively) and general disorders and administration site conditions (8.0% *versus* 5.2%, respectively), and vascular disorders more frequently reported in the SrRan 1g group than in the placebo group (17.9 *versus* 15.3%, respectively).
The most commonly reported emergent adverse events were osteoarthritis (16.4% in the SrRan 1g group, 16.7% in the SrRan 2g group and 17.3% in the placebo group) hypertension (10.9%, 12.8% and 11.3%, respectively) and arthralgia (9.5%, 11.7%, and 10.8%, respectively). No relevant between-group differences were detected except an increased frequency in the SrRan 2g group compared to placebo for diarrhoea: 7.8% *versus* 4.3%, respectively, hypercholesterolemia: 7.3% *versus* 4.0%, and pneumonia: 3.0% *versus* 1.1%, respectively.
Emergent adverse events reported during the study with SrRan 2g were in accordance with the expected known events.

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

Most emergent adverse events were graded as mild or moderate (94.6% of the events). **Severe emergent adverse events** occurred in 72 patients (13.1%) in the SrRan 1g group, 91 patients (16.1%) in the SrRan 2g group and 80 patients (14.4%) in the placebo group. No relevant between-group differences were detected as regards the nature and the frequency of these severe events.

Most of the EAE recovered or were recovering/improving or recovered with sequelae (74.3% of the events in the SrRan 1g group, 74.9% in the SrRan 2g group and 74.5% in the placebo group). 5 EAEs led to death: 1 patient in the SrRan 1g group (histiocytosis haematophagic), 1 patient in the SrRan 2g group (sudden death) and 3 patients in the placebo group (general physical health deterioration, motor neuron disease, gastric cancer).

Treatment-related emergent adverse events were reported in 487 patients: 156 patients (28.5%) in the SrRan 1g group, 183 patients (32.4%) in the SrRan 2g group and 148 patients (26.6 %) in the placebo group. The system organ classes most commonly affected in the three groups were gastrointestinal disorders (13.0% in the SrRan 1g group, 15.8% in the SrRan 2g group and 12.4% in the placebo group) and skin and subcutaneous tissue disorders (4.4%, 6.2% and 4.9%, respectively).

The frequency of patients who reported at least **one emergent adverse event leading to treatment discontinuation** was higher in the SrRan 2g group than in the other groups: 20.7% *versus* 16.6% in the SrRan 1g group and 16.2% in the placebo group. This higher percentage in the SrRan 2g group was mainly attributable to skin and subcutaneous tissue disorders (2.4% in the SrRan 1g group, 5.1% in the SrRan 2g group and 2.5% in the placebo group). Among skin disorders, rash pruritic (reported in 0.5%, 1.1% and 0.7% of the patients, respectively) and allergic dermatitis (reported in 0.4%, 0.7% and 0.4% of the patients, respectively) were the most frequently associated with premature treatment discontinuation. The other most commonly affected system organ classes were gastrointestinal disorders (6.2%, 4.8% and 5.6%, respectively), mainly diarrhoea (1.1%, 1.6%, and 1.4%, respectively) and musculoskeletal and connective tissue disorder (1.5%, 3.4% and 2.0%, respectively), mostly osteoarthritis (0.4%, 0.9%, and 0.5%, respectively).

Emergent serious adverse events were reported in 283 patients with a similar frequency in the 3 treatment groups: 93 patients (17.0%) in the SrRan 1g group, 93 patients (16.5%) in the SrRan 2g group and 97 patients (17.4%) in the placebo group. The most frequently affected system organ classes were musculoskeletal and connective tissue disorders (3.3%, 5.0% and 4.1%, respectively), including mostly osteoarthritis (2.2%, 3.2% and 3.1%, respectively), neoplasm benign, malignant and unspecified (incl. cysts and polyps) (2.9%, 2.5% and 2.7%, respectively) and cardiac disorders (1.6%, 2.7% and 1.1%, respectively). A total of 21 serious emergent adverse events were considered as treatment-related by the investigator: 8 events in each of the SrRan groups and 5 events in the placebo group.

During the treatment period, **11 VTE**: 6 cases of deep vein thrombosis (DVT) and 5 cases of pulmonary embolism (PE) were reported in 9 patients:
- 5 patients in the SrRan 1g group: 3 patients had one DVT, one patient had one PE, and one patient had both one DVT and one PE.
- 3 patients in the SrRan 2g group: 2 patients had one PE and one patient had one DVT.
- 1 patient in the placebo group reported both one DVT and one PE.

The VTEs were considered as treatment-related according to the investigator except for one patient in the SrRan 1g group for which the event followed a post-operative immobilisation, and one patient in the SrRan 2g group, following air travel.

Moreover, after the study treatment period, one pulmonary thrombosis occurred 134 days after the last study drug intake in the SrRan 2g group, considered as treatment-related according to the investigator.

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

Overall, **10 patients died** (3 in each SrRan group, and 4 in the placebo group), all considered as not-treatment related.
6 deaths were rerorted **during the study**: 3 in the SrRan 1g group, 2 in the SrRan 2g group, and 1 in the placebo group.
- Two of these deaths occurred during the treatment period: histiocytosis haematophagic in the SrRan 1g group and general physical health deterioration in the placebo group.
- Four deaths occurred after the treatment period: cerebral haemorrhage and myocardial infarction in the SrRan 1g group (3 months and 28 months after the last study drug intake, respectively), multi-organ failure and sudden death in a patient having a pre-existing metastatic lung cancer in the SrRan 2g group (about 2 months and 67 days after the last study drug intake, respectively).

Moreover, 4 patients died **after the study period**: 1 patient in the SrRan 2g group (4 months after the last study drug intake) and 3 patients in the placebo group, all considered as not treatment-related.

Laboratory safety tests
Neither clinically relevant changes over time nor differences between the three groups were detected. Some between-group differences were observed for CPK, calcium and phosphorus. Mean CPK levels increased from baseline to end in both SrRan groups (mean ± SD = 11.7 ± 85.6 IU/L in the SrRan 1g group and 20.7 ± 104.4 IU/L in the SrRan 2g group) whereas it remained stable in the placebo group (mean ± SD = -0.4 ± 68.1 IU/L). High emergent out-of-reference-range values for CPK were more frequently reported in the SrRan groups than in the placebo group: 17.6% in the SrRan 1g group, 19.4% in the SrRan 2g group *versus* 10.6% in the placebo group. Most of these patients had abnormal CPK values in the]1x – 2x] upper limit of the normal (ULN) range (93.3% of patients in the SrRan 1g group, 85.0% in the SR 2g group, and 87.3% in the placebo group). CPK values were in the]2 – 3] X ULN range for 1.1%, 10%, and 5.5% of the patients, respectively. CPK values between 3 and 5 ULN affected few patients in any group, and values above 5 ULN were detected in 3.3% (3 patients), 1.0% (1 patient), and 7.3% (4 patients), respectively, of the patients having abnormal values.
In both SrRan groups, slight changes were observed in phosphocalcic homeostasis parameter: decrease in blood calcium and increase in blood phosphorus.
Emergent (PCSA) were sparse (< 5% in any group) except for the following parameters for which high PCSA values were more frequently reported in the SrRan treatment groups than in the placebo group:
- C-reactive protein: 20.2% in the SrRan 1g, 22.5% in the SrRan 2g *versus* 16.0% in the placebo group, respectively.
- Phosphorus: 8.6%, 20.0% *versus* 3.1%, respectively.

Neither clinically relevant changes nor differences between the three groups were detected for mean changes in haematological or hemostasis parameters, except for factor VIII, for which the mean (± SD) increase from baseline to end was higher in both SrRan groups compared to placebo group: 14.1 ± 38.4 % in the SrRan 1g, 21.8 ± 43 % in the SrRan 2g *versus* 10.1 ± 41.4 % in the placebo group). Emergent PCSA were sparse except for the following parameters for which high PCSA values were more frequently reported in the SrRan groups than in the placebo group:
- Prothrombin fragment 1+2: 14.4% in the SrRan 1g group, 15.8% in the SrRan 2g group, and 12.2% in the placebo group.
- Factor VIII: 4.8%, 8.5%, and 3.0%, respectively.
- Fibrinogen: 3.9%, 4.9% *versus* 1.3%, respectively.

Vital signs
Neither clinically relevant changes over time nor differences between groups were detected for vital signs.

Name of Company: I.R.I.S. 50 rue Carnot 92284 – Suresnes Cedex - FRANCE	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Protelos® Osseor® (Europe)	Volume:	
Name of Active Ingredient: Strontium ranelate (S 12911)	Page:	

CONCLUSION

This international double-blind controlled study, conducted in 1683 male or female patients aged ≥ 50 years with primary knee osteoarthritis, demonstrated the superiority of a 3-year treatment with strontium ranelate 1g and 2g daily over placebo in reducing radiographic progression of knee osteoarthritis. The mean loss in joint space width (primary efficacy criterion) was significantly reduced in patients treated with SrRan 1g and 2g as compared to those treated with placebo: the difference *versus* placebo was of 0.14 mm (p < 0.001) in favour of SrRan 1g and 0.10 mm (p = 0.018) in favour of SrRan 2g. The reduction in JSW loss was not significantly different between the two doses of SrRan tested (1g and 2g).

The analysis of individual joint space narrowing showed that significantly fewer patients in the SrRan groups than in the placebo group had radiographic failure (JSN ≥ 0.5 mm): 22.3% of the patients in the SrRan 1g group (p < 0.001), 25.6% in the SrRan 2g group (p = 0.012) *versus* 33.1% in the placebo group. Radiological and radioclinical progression of the OA was lower in the SrRan groups than in the placebo group, with a statistically significant between-group difference.

This finding supports the clinical benefit of the treatment with SrRan, since the reduced loss of JSW has been shown to be predictive of better OA outcomes including a decreased risk of undergoing osteoarthritis related joint surgery during the ensuing 5 years.

The structure-modifying effects observed with both doses of SrRan were associated, for the SrRan 2g dose, with improvements in symptoms of osteoarthritis as evaluated by the WOMAC global score and pain subscore for the target knee. A general trend in favour of SrRan 2g was also found for algo-functional assessments of the hand (AUSCAN) and the hip (VAS pain scale).

The overall incidence of emergent adverse events and of serious emergent adverse events was similar in the three treatment groups. The safety profile of SrRan 2g/day in patients with OA was similar with that previously described in osteoporotic patients. Venous thromboembolic events were infrequent, but were more frequent with strontium ranelate than with placebo. Clinical laboratory evaluation yielded expected results: slight changes in CPK and phosphocalcic homeostasis parameters, and revealed no new or unexpected biological concerns.

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