Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**A 24 months, prospective, randomised double-blind study to assess the effect of daily oral administration of 2 g of strontium ranelate *versus* placebo on bone mineral density in postmenopausal osteoporotic women previously treated with bisphosphonates (following Amendment No. 4, instead of oral bisphosphonates initially planned in the study protocol).**
Test drug code	**Strontium ranelate (S12911)** **Protelos®**
Indication	**Post-menopausal osteoporosis**
Development phase	**Phase III**
Protocol code	**CL3-12911-038**
Study initiation date	**8 November 2011**
Study completion date	**26 June 2014**
Main coordinator	[redacted]
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France**
Responsible medical officers	[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	**6 January 2015**
Version of the report	**Final version**
	~~**CONFIDENTIAL**~~

2. SYNOPSIS

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

Title of study: A 24 months, prospective, randomised, double-blind study to assess the effect of daily oral administration of 2 g of strontium ranelate *versus* placebo on bone mineral density in postmenopausal osteoporotic women previously treated with bisphosphonates (following Amendment No. 4, instead of oral bisphosphonates initially planned in the study protocol).

Protocol No.: CL3-12911-038
EudraCT No.: 2011-000708-17
The description of the study protocol given hereafter includes the modifications of the 8 substantial Amendments to the protocol.

International coordinator : [redacted]

Study centres:
In all, 9 centres located in 6 countries included a total of 83 patients: Austria (1 centre, 4 patients), Belgium (1 centre, 3 patients), France (1 centre, 1 patient), Germany (1 centre, 53 patients), Hungary (2 centres, 11 patients), Poland (3 centres, 11 patients).

Publication (reference): Not Applicable

Studied period:	**Phase of development of the study:**
Initiation date: 8 November 2011 Completion date: 26 June 2014	phase III

Objectives:

Primary objective:
The primary objective was to demonstrate the effect of daily oral administration of 2 g of strontium ranelate *versus* placebo over 24 months of treatment on the lumbar areal bone mineral density in postmenopausal women with osteoporosis previously treated with bisphosphonates (instead of "oral bisphosphonates", as per Amendment No. 4).

Secondary objectives:
The secondary objectives aimed to evaluate the effects of strontium ranelate *versus* placebo over 24 months of treatment in postmenopausal women on with osteoporosis previously treated with bisphosphonates on:

- Areal bone mineral density (BMD) of the total hip and femoral neck (DXA-BMD).
- Bone geometry and parameters of bone strength at different tibia and radius sites (pQCT) in a subgroup of patients in Germany only, as specified in Amendment No. 5.
- Bone turnover (biochemical bone markers).
- Th12 volumetric bone mineral density and parameters of bone structure (Hr-QCT) in a subgroup of patients in the International Coordinator's centre, as specified in Amendment No. 5.

and to assess the clinical and biological safety of this treatment including vertebral fracture incidence (VFA).

Methodology:
This study was an international, multicentre (following Amendment No. 5, instead of monocentre study initially planned in the study protocol), prospective, randomised, double-blind, parallel-group, placebo-controlled phase III study. The treatments (strontium ranelate or placebo) were to be assigned at inclusion by a balanced randomisation (ratio 1:1) using stratification on the centre.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.
As the study has been prematurely stopped due to difficulties in patients' recruitment, an abbreviated report was written.

Number of patients:
Planned: 160 patients, 80 in the strontium ranelate (SrRan) group and 80 in the placebo group.
Included: 83 patients, 39 in the SrRan group and 44 in the placebo group.
Due to difficulties in patient's recruitment, the number of included patients was much lower than initially planned.

Diagnosis and main criteria for inclusion:
Women of at least 50 years of age (with no upper age limit), postmenopausal for at least 5 years, with osteoporosis in patients at high risk for fracture (as added by to Amendment No. 6), with:

- Previous bisphosphonate therapy for at least 30 months* among the last 5 years (initially at least 24 continuous months updated to at least 36 continuous months by Amendment No 2, then modified to 30 months among the last 5 years following Amendment No. 4) (at least 60 months* for Austria, as added by Amendment No. 8) before study entry, and,
- Last bisphosphonate intake within 6 months before study entry (instead of within 2 months before study entry, following Amendment No. 4). Bisphosphonate therapy includes:
  - Oral alendronate (70 mg once weekly or 10 mg daily, or as specified by Amendment No. 5 an equivalent dosage), oral risedronate (35 mg once weekly or 5 mg daily, or as specified by Amendment No. 5 an equivalent dosage),
  - Oral ibandronate (150 mg once monthly) or intravenous ibandronate (3 mg/3 months), as added by Amendment No. 4.

** As added by Amendment No. 2, an adequate previous bisphosphonate treatment required an estimated "recent" medication possession ratio (MPR) of at least 75% (instead of 80% following Amendment No. 4) in the last year of bisphosphonate treatment.*

Test drug:
Strontium ranelate 2 g administered orally as one sachet of granules taken daily at bedtime. In addition, patients received a supplementation of elementary calcium 500 mg/day and oral non-hydroxylated vitamin D 1000 IU/day taken at lunchtime (to be adapted to the specific needs of the patient).
Batch Nos.: L0037906, L0041885, L0044868.

Comparator (Reference product and/or placebo):
Matching placebo administered orally as one sachet of granules taken daily at bedtime. As specified above a supplementation of calcium and oral non-hydroxylated vitamin D was provided.

Duration of treatment:
Run-in period: 1-4 weeks from selection visit (ASSE) to inclusion visit (M0).
Double-blind treatment period: 2 years, with 5 follow-up visits (M3, M6, M12, M18 and M24).

Criteria for evaluation:

Efficacy measurements:
Primary efficacy criterion:
The primary assessment criterion was the lumbar areal BMD (L1-L4) (g/cm²) assessed by Dual energy X-ray Absorptiometry (DXA) over 24 months of treatment, expressed as value at each visit. A standardised assessment was performed at each centre, and a central reading was done (Charité, Berlin, Germany). Due to the premature discontinuation of the study, only descriptive statistics at each visit were performed and no efficacy analyses were carried out on secondary criteria, according to the Statistical Analysis Plan.

Safety measurements:
- Adverse events were reported at each visit.
- Laboratory tests (biochemistry / haematology parameters) were performed at ASSE, M6, M12, M18 and M24 (evaluations at M6 and M18 were added by Amendment No. 6), except 25-OH-vitamin D and parathyroid hormone intact parameters only assessed at ASSE.
- Clinical examination (weight, height) was assessed at ASSE, M12, and M24.
- Vital signs: blood pressure (sitting systolic (SBP) and diastolic blood pressure (DBP)) were assessed at each visit (evaluations at M3, M6 and M18 were added following Amendment No. 6) and heart rate (HR) was measured at ASSE, M0, M12 and M24.
- Vertebral Fracture Assessment was assessed at ASSE, M12 and M24 by DXA.

Pharmacokinetic measurements:
Not applicable.

Statistical methods:
Analysis Set:

Efficacy analysis:
Primary criterion:
Descriptive statistics for efficacy analysis was carried out on the Randomised Set (included patients to whom a therapeutic unit was randomly assigned at M0), over 24 months.
Of note, the one-year statistical analysis initially planned in the study protocol was not performed due to the premature stop of the study.

Study outcome analysis: descriptive statistics were provided in the Randomised Set (and in Safety Set for some parameters).
Safety analysis: descriptive statistics were provided in the Safety Set.

SUMMARY - CONCLUSIONS
DISPOSITION OF PATIENTS AND ANALYSIS SETS

Disposition of randomised patients by group

Status		SrRan 2 g (N = 39)	Placebo (N = 44)	All (N = 83)
Included/randomised	**n**	**39**	**44**	**83**
In compliance with the protocol	n (%)	36 (92.3)	39 (88.6)	75 (90.4)
With a protocol deviation before or at inclusion	n (%)	3 (7.7)	5 (11.4)	8 (9.6)
Withdrawn due to	**n (%)**	**14 (35.9)**	**16 (36.4)**	**30 (36.1)**
Lack of efficacy	n (%)	1 (2.6)	9 (20.5)	10 (12.0)
Protocol deviation*	n (%)	5 (12.8)	4 (9.1)	9 (10.8)
Adverse event	n (%)	6 (15.4)	-	6 (7.2)
Non-medical reason	n (%)	2 (5.1)	3 (6.8)	5 (6.0)
Lost to follow-up	n (%)	-	-	-
Ended due to study termination**	**n (%)**	**18 (46.2)**	**25 (56.8)**	**43 (51.8)**
In compliance with the protocol	n (%)	16 (41.0)	19 (43.2)	35 (42.2)
With a protocol deviation after inclusion	n (%)	2 (5.1)	6 (13.6)	8 (9.6)
Completed	**n (%)**	**7 (17.9)**	**3 (6.8)**	**10 (12.0)**
In compliance with the protocol	n (%)	6 (15.4)	2 (4.5)	8 (9.6)
With a protocol deviation after inclusion	n (%)	1 (2.6)	1 (2.3)	2 (2.4)
Randomised Set (RS)	**n**	**39**	**44**	**83**
Safety Set (SS)	**n (%)**	**39 (100)**	**44 (100)**	**83 (100)**

N: Number of patients by group; n: Number of patients; %: Expressed as percentage of the patients from the Randomised Set
**: Among patients withdrawn due to protocol deviations, 5 (3 in the SrRan group and 2 in the placebo group) were withdrawn due to cardiac contraindication added by Amendment No. 6, in order to comply with the update of the Summary of Products Characteristics (SmPC) (patient Nos. 038 276 0001 00014, 038 276 0001 00016, 038 276 0001 00017, 038 276 0001 00019, 038 276 0001 00060).*
***: Patients counted in the category "ended due to study termination" correspond to on-going patients withdrawn from the study due to the premature study discontinuation.*

A total of 83 were included and randomly assigned to one of the 2 groups: 39 patients in the SrRan group and 44 in the placebo group. The planned balanced distribution was reached, despite a number of patients included lower than planned.

In the Randomised Set, 30 patients (36.1%) were withdrawn, without relevant difference between groups (14 patients, 35.9% *versus* 16 patients, 36.4%, respectively), mainly due to lack of efficacy (10 patients, 12.0%) with a lower rate in the SrRan group (1 patient, 2.6%) than in the placebo group (9 patients, 20.5%). In the SrRan group, the main reason for withdrawal was adverse event (6 patients, 15.4% *versus* none in the placebo), mainly gastrointestinal disorders (2 patients, 5.1%). It is to note that one patient in the SrRan group was withdrawn for an emergent serious Venous ThromboEmbolism (VTE): pulmonary embolism, which was not considered as treatment-related by the investigator (but due to a nephrotic syndrome). This VTE was upgraded as treatment-related by the Sponsor. A total of 43 (51.8%) on-going patients ended the study due to the premature study discontinuation, with a lower rate in the SrRan group than in the placebo group (18 patients, 46.2% *versus* 25 patients, 56.8%, respectively). In all, 10 patients (12.0%) completed the study, with a higher rate in the SrRan group than in the placebo group: 7 patients (17.9%) *versus* 3 patients (6.8%), respectively. No patient was lost to follow-up.

SUMMARY – CONCLUSIONS (Cont'd)

DISPOSITION OF PATIENTS AND ANALYSIS SETS (Cont'd)

In all, 11 protocol deviations in 8 patients (9.6%) were observed before or at inclusion. The most frequent deviations concerned study management (8 patients, 9.6% *i.e.* 3 patients, 7.7% in the SrRan group *versus* 5 patients, 11.4% in the placebo group), mostly due to a delay in DXA examination greater than 4 weeks between selection and inclusion: one patient (2.6%) in the SrRan group *versus* 3 patients (6.8%) in the placebo group.

After inclusion, 39 protocol deviations were observed in 26 patients (31.3%), with similar frequency in both treatment groups (12 patients, 30.8% *versus* 14 patients, 31.8%, respectively). The most frequent deviations concerned study management (18 patients, 21.7%), without relevant difference between groups (9 patients in each treatment group, 23.1% *versus* 20.5%, respectively), mainly due to study medication administration with a higher rate reported in the SrRan group than in the placebo group (8 patients, 20.5% *versus* 6 patients, 13.6%, respectively).

BASELINE CHARACTERISTICS

Demographics and other baseline characteristics in the Randomised Set were globally in accordance with the target population.
Patients (all women) were on average 70.0 ± 6.7 years old, and mostly ≥ 70 years, with a higher frequency reported in the SrRan group than in the placebo group (64.1% *versus* 56.8%, respectively).
All patients were diagnosed as having osteoporosis before entry in the study. Among them, 22 (26.5%) reported at least one previous osteoporotic vertebral fracture and 17 (20.5%) reported at least one previous osteoporotic peripheral fracture. A family history of osteoporosis was reported in 24 patients (30.0%), and 7 patients (8.5%) reported a history of hip fracture in one parent. No relevant difference between groups was detected.
Among the 83 included patients, 82 received at least one previous treatment for osteoporosis (and/or likely to interfere with bone metabolism) that was discontinued at study entry, and one patient in the SrRan group received one previous treatment for osteoporosis (bisphosphonate) that was not discontinued at selection (and considered as having protocol deviation).
The previous treatments received for osteoporosis consisted mainly in bisphosphonates, with a higher frequency reported in the SrRan group than in the placebo group (36 patients, 92.3% *versus* 38 patients, 86.4%, respectively). The overall mean treatment duration for previous treatments containing bisphosphonates was 75.1 ± 37.1 months, ranging from 29.7 to 224.7 months. All patients (except one) had taken previous treatments containing bisphosphonates for at least 30 months, and more than half of them (57.3%) had taken these treatments during at least 60 months. No relevant difference between groups was observed.

At inclusion, most patients (91.6%) had taken at least one **concomitant treatment**. The most frequent were agents acting on the renin-angiotensin system, less frequently reported in the SrRan group than in the placebo group: 12 patients, 30.8% *versus* 18 patients, 40.9%, respectively.

Efficacy parameter at baseline was similar in the two treatment groups. The mean baseline **lumbar L1-L4 BMD** was 0.829 ± 0.098 g/cm^2, and the mean T-score was -2.93 ± 0.82. Most patients were osteoporotic at the lumbar site (*i.e.* T-score : < -2.5): 55 patients, 66.3%, and one third were osteopenic (*i.e.* T-score: [-2.5; -1]): 27 patients, 32.5%. As regards others sites, the mean total hip BMD was 0.763 ± 0.100 g/cm^2 (mean T-score was -1.98 ± 0.83) and the mean femoral neck BMD was 0.728 ± 0.114 g/cm^2 (mean T-score was -2.10 ± 0.95).

No relevant between-group difference was detected for **vital signs and physical examination**. The mean values were for SBP: 130.6 ± 15.9 mmHg, DBP: 77.2 ± 8.1 mmHg, HR: 74.5 ± 7.7 bpm, weight: 64.2 ± 10.0 kg, height: 159.5 ± 6.0 cm, and body mass index (BMI): 25.2 ± 3.6 kg/m^2.

EXTENT OF EXPOSURE

The mean total **treatment duration** was 368.2 ± 236.1 days (ranging from 26 to 736 days), and was higher in the SrRan group than in the placebo group: 406.9 ± 251.6 days (median = 467.0 days) *versus* 334.7 ± 219.3 days (median = 235.0 days), respectively, in the Randomised Set. Total **exposure to treatment** showed similar trends than the treatment duration, indicating that few treatment interruptions occurred. The mean **compliance** was good: 91.9 ± 12.6% (median 96.0%), and ranged from 24 % to 104 %, without any relevant difference between groups. The compliance was comprised in the [80 ; 120]% range for 91.6 % of patients, with a lower rate of patients in the SrRan group than in the placebo group *(*84.6% *versus* 97.7%, respectively).

SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Due to the premature stop of the study, only descriptive statistics (at each visit) for the primary criterion (lumbar areal BMD (L1-L4) (g/cm²) was provided in the Randomised set.

- **Primary assessment criterion**

No relevant difference between groups was observed at each visit (M6, M12, M18 and M24).
The lumbar L1-L4 BMD (g/cm²) was 0.860 ± 0.098 g/cm² at M12 (n = 22 patients) and 0.877 ± 0.094 g/cm² at M24 (n = 6 patients) in the SrRan group *versus* 0.863 ± 0.085 g/cm² at M12 (n = 21 patients) and 0.893 ± 0.018 g/cm² at M24 (n = 3 patients) in the placebo group, in the Randomised Set.

SAFETY RESULTS

Adverse events

Summary of adverse events - Safety Set

		SrRan 2 g (N = 39)	Placebo (N = 44)
Patients having reported			
at least one emergent adverse event	n (%)	35 (89.7)	30 (68.2)
at least one treatment-related emergent adverse event	n (%)	5 (12.8)	2 (4.5)
Patients having experienced			
at least one serious emergent adverse event (including death)	n (%)	11 (28.2)	8 (18.2)
at least one treatment-related serious adverse event	n (%)	1 (2.6)	-
Patients with treatment withdrawal			
due to an EAE	n (%)	6 (15.4)	-
due to an serious EAE	n (%)	3 (7.7)	-
due a treatment-related EAE	n (%)	2 (5.1)	-
due a treatment-related serious EAE	n (%)	1 (2.6)	-
Patients who died	n (%)	-	-

N: number of patients in each treatment group considered; n: number of patient by category; %: (n/N) x100.

Overall 65 patients (78.3%) reported at least one emergent adverse event (EAE), with a higher rate reported in the SrRan group (35 patients, 89.7%) than in the placebo group (30 patients, 68.2%). The between-group difference was mainly due to Gastrointestinal disorders (14 patients, 35.9%, in the SrRan group *versus* 11 patients, 25.0% in the placebo group).

In the SrRan group, the most frequently affected **system organ classes (SOCs)** (*i.e.* those affecting more than 20% of patients in any treatment group) were reported with a larger frequency in the SrRan group than in the placebo group: Infections and infestations (17 patients, 43.6% in the SrRan group *versus* 16 patients, 36.4% in the placebo group), and Gastrointestinal disorders (see above). In addition, the others SOCs reported with a higher frequency in the SrRan group than in the placebo group were: Psychiatric disorders (5 patients, 12.8% *versus* 2 patients, 4.5%, respectively), and Ear and labyrinth disorders (3 patients, 7.7% *versus* none, respectively).

In the SrRan group, the most frequent **EAEs** (*i.e.* those affecting more than 10% of patients in any treatment group) were: nasopharyngitis (10 patients, 25.6% in the SrRan group *versus* 10 patients, 22.7% in the placebo group), back pain, with a larger frequency reported in the SrRan group than in the placebo group (6 patients, 15.4% *versus* 4 patients, 9.1%, respectively), fall (5 patients, 12.8% *versus* 7 patients, 15.9%, respectively), and bronchitis (5 patients, 12.8% *versus* 4 patients, 9.1%, respectively). The other EAEs reported with a higher frequency in the SrRan group than in the placebo group were: abdominal distension, carpal tunnel syndrome, paraesthesia, depression, and hypothyroidism (each 2 patients, 5.1% in the SrRan group *versus* none in the placebo group).

As regards the **important identified risks** of the strontium ranelate, one case of Venous ThromboEmbolism was reported in the SrRan group. This serious EAE, was a pulmonary embolism, not considered as treatment-related by the investigator (but due to a nephrotic syndrome), that led to drug withdrawal, and resolved. Of note, this event was upgraded as treatment-related by the Sponsor. There was no case of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome or myocardial infraction reported in this study.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Most of the EAEs were rated **mild**, without relevant difference between groups (42.5% *versus* 44.6% of the total EAEs), or **moderate** with a higher frequency reported in the SrRan group than in the placebo group (45.8% *versus* 39.0%, respectively).

Overall, 26 patients (31.3%) reported at least one **severe EAE,** without relevant difference between groups: 12 patients, 30.8% *versus* 14 patients, 31.8%, respectively. In the SrRan group, the most frequent SOC affected was Injury, poisoning and procedural complications, with a higher frequency reported in the SrRan group than in the placebo group (5 patients, 12.8% *versus* 2 patients, 4.5%, respectively), including mostly fall (3 patients, 7.7% *versus* 2 patients, 4.5%, respectively). All other severe EAEs were reported once except the following in the placebo group: bronchitis, osteoarthritis and respiratory tract infection (each 2 patients, 4.5%), and gastroenteritis (3 patients, 6.8%). No severe EAE was considered as treatment-related by the investigator.

Emergent AEs considered as treatment-related according to the investigator's opinion were reported with a higher frequency in the SrRan group than in the placebo group (5 patients, 12.8% *versus* 2 patients, 4.5%, respectively). They affected mainly Gastrointestinal disorders (5 patients, 12.8% *versus* none, respectively). Treatment-related EAEs did not affect particular preferred term.

In all, 6 patients (15.4%) in the SrRan group experienced 8 **EAEs that led to treatment withdrawal** *versus* none in the placebo group. The most frequently affected SOC was Gastrointestinal disorders: 4 EAEs were reported in 2 patients (5.1%). No particular preferred term was affected.

A **recovery or a recovering** was observed for most of the EAEs, with a higher frequency reported in the SrRan group than in the placebo group: 80.4% *versus* 71.8%, respectively.

Serious EAEs (SEAEs) were reported with a higher frequency in the SrRan group than in the placebo group (11 patients, 28.2% *versus* 8 patients, 18.2%, respectively). In both groups, the most frequently affected SOC was Surgical and medical procedures (2 patients, 5.1% *versus* 2 patients, 4.5%), with no particular preferred term affected. Among the 26 SEAEs, one in the SrRan group (*versus* none in the placebo) was considered as treatment-related according to the investigator's opinion: gastritis erosive (that led to treatment withdrawal, and resolved).
Serious EAEs led to treatment withdrawal in 3 patients (3.6%), all in the SrRan group: pulmonary embolism, gastritis erosive, and invasive ductal breast carcinoma. All of these patients recovered except one that did not recover at the end of the study (invasive ductal breast carcinoma).
No **death** was reported in this study.

Biochemical **emergent Potentially Clinically Significant Abnormal values (PCSA)** were reported in 2 patients in each treatment group for the following parameters: high GGT value (one patient, 2.9% in the SrRan group *versus* 2 patients, 4.6% in the placebo group) and low albumin value (one patient, 2.9% *versus* none, respectively), in the safety Set.
Haematological emergent PCSA values were detected only in the placebo group (2 patients, 4.5%) for the following parameters: white blood cells (one low value in one patient) and basophils (one high value in one patient).

As regards **vital signs and physical examination**, no relevant difference between groups was observed for weight, DBP and heart rate. As regards SBP, a slight difference in mean value at the end of treatment was observed between groups: 138.8 ± 17.2 mmHg in the SrRan group *versus* 133.0 ± 15.8 mmHg in the placebo group.

New or worsening **vertebral fractures** (defined as new or worsening at visit M12 or M24, if the grade of the vertebral fracture at the visit M12 or M24 was above the grade observed at the previous visit) were reported in 2 patients (5.1%) in the SrRan group and 3 patients (6.8%) in the placebo group, in the safety set. All these deformities were new and were due to osteoporosis.

CONCLUSION

This international double-blind placebo-controlled phase III study was conducted in 83 postmenopausal osteoporotic women previously treated with bisphosphonates, instead of the 160 initially planned. The study was prematurely discontinued, due to difficulties in patients' recruitment. Thus, the study lasted at maximum 2 years, with a mean of about one year. Due to the low number of patients who completed the study at 24 months (n = 10), only descriptive analyses have been performed. No relevant between-group (strontium ranelate (SrRan) *versus* placebo) difference was observed for the lumbar L1-L4 BMD (primary efficacy criterion) at M24.

Regarding safety, emergent adverse events were more frequently reported in the SrRan group than in the placebo group (89.7% *versus* 68.2%, respectively), mainly due to Gastrointestinal disorders. With regards to important identified risks of the strontium ranelate, one case of serious emergent pulmonary embolism was reported in the SrRan group, not considered as treatment-related by the investigator, but due to a nephrotic syndrome. No case of emergent Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson syndrome, Toxic Epidermal Necrolysis (TEN), or myocardial infarction was reported. Five patients reported new vertebral fracture: 2 patients in the SrRan group and 3 patients in the placebo group.

Date of the report: 6 January 2015

Version of the report: Final version