Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Knee joint replacement over 5 years in patients with knee osteoarthritis. A long term follow-up study in patients of the CL3-12911-018 study.**
Test drug code	**No study drug**
Indication	**Osteoarthritis**
Development phase	**Phase III**
Protocol code	**CL3-12911-040**
Study initiation date	**19 March 2012 (date of the first visit of the first patient)**
Study completion date	**30 June 2014 (date of the last visit of the last patient)**
Main coordinator	[redacted]
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex – France** **Servier Canada** **235, Armand Frappier Blvd.** **H7V 4A7 Laval - Canada** **Laboratorios Servier S.L.** **Avenida de los Madronos 33 Parque del Conde de Orgaz** **28043 Madrid - Spain** **Les Laboratoires Servier** **Paveletskaya Sq, 2-3** **15054 Moscow - Russia** **Servier UK** **Servier Research & Development,** **Rowley, Wexham Springs, Framewood Road, Wexham,** **Slough, SL3 6PJ - United Kindom**
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	**04 November 2014**
Version of the report	**Final version**
	~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** No study drug received **Name of Active Ingredient:** No study drug received		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: Knee joint replacement over 5 years in patients with knee osteoarthritis. A long term follow-up study in patients of the CL3-12911-018 study. Protocol No: CL3-12911-040 EudraCT No.: 2011-004046-18		
International coordinator [redacted]		
Study centres: International, multicentre study: 75 centres located in 18 countries included 878 patients: Australia (5 centres – 21 patients included), Austria (3 centres - 27 patients included), Belgium (5 centres – 69 patients included), Canada (6 centres – 149 patients included), Czech Republic (2 centres – 23 patients included), Denmark (3 centres – 151 patients included), Estonia (1 centre – 26 patients included), France (16 centres – 42 patients included), Germany (4 centres – 21 patients), Italy (7 centres – 68 patients), Lithuania (1 centre – 5 patients), The Netherlands (2 centres – 12 patients), Poland (3 centres – 71 patients), Portugal (2 centres – 4 patients), Romania (1 centre – 7 patients), Russian Federation (5 centres – 39 patients), Spain (7 centres – 96 patients), United Kingdom (3 centres – 47 patients).		
Publication (reference): Not applicable.		
Studied period: Initiation date: 19 March 2012 (date of first visit first patient). Completion date: 30 June 2014 (date of last visit last patient).	**Phase of development of the study:** Phase III	
Objectives: The objectives were to collect data on knee joint replacement procedures or procedures practiced in the knee (arthroscopy, osteotomy or other) over 5 years in patients with knee osteoarthritis having participated in the CL3-12911-018 study and having received at least one year (365 days) of CL3-12911-018 study treatment (strontium ranelate 1 g/2 g or placebo).		
Methodology: International, multicentre, follow-up study over 5-year, conducted in patients having participated in the previous CL3-12911-018 study, and having received at least one year of treatment (strontium ranelate 1 g/2 g or placebo). No study drug was received by the patients in the present study. This study did not affect the physician's decision regarding the treatment to use on each individual patient. Available drugs for osteoarthritis (OA) treatment were prescribed by the investigator as needed, solely as a result of a normal clinical evaluation. There was no modification of the medical practice of the participating investigators, and no additional extra routine examinations for the patients. An abbreviated report was written, as the study was prematurely ended following the Sponsor decision for strategic reason.		
Number of patients: **Planned**: 1206 patients. **Included**: 878 patients: 288 patients in the former strontium ranelate (SrRan) 1 g group, 296 patients in the former SrRan 2 g group and 294 patients in the former placebo group. *Note: the patients were presented according to the treatment group they received during the CL3-12911-018 study, i.e. called in the present study former SrRan 1 g or 2 g group, or former placebo group.*		
Diagnosis and main criteria for inclusion: Patients with a primary knee OA included in the CL3-12911-018 study and having received the CL3-12911-018 study treatment (either strontium ranelate 1 g/2 g or placebo) for at least one year.		
Test drug: Not applicable.		

Comparator (Reference product and/or placebo):
Not applicable.

Duration of treatment:
Study period without any study drug received by the patients:

- Inclusion visit (M0).
- Follow-up period, with 5 phone calls at M12, M24, M36, M48 and M60 visits (± 3 months time window).

Criteria for evaluation:
Efficacy measurements
Evaluation criteria: knee joint replacement (total prosthesis or partial prosthesis) of the knee followed during the CL3-12911-018 study, and the knee surgery or other procedures (arthroscopy, osteotomy or other).

Safety measurements: weight reported at each visit.

Statistical methods:

Study outcome: descriptive statistics were provided.

Efficacy analyses were performed in the Included Set follow-up (defined as all randomised patients in the CL3-12911-018 study who were included in the follow-up study).
Descriptive statistics were provided in each former treatment group on:

- Number of patients with at least one knee joint replacement (total or partial prosthesis).
- Total number of knee joint replacement (total or partial prosthesis).

A listing of patients with a knee surgery or procedure: knee joint replacement, other knee surgery (arthroscopy, osteotomy) or other procedure was also provided.

Safety analysis: descriptive statistics were provided for the weight.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Disposition of patients

STATUS	Former SrRan 1 g	Former SrRan 2 g	Former Placebo	All
Patients included in the CL3-12911-018 study *				**1206**
No contact information or not contacted				**187**
Contacted	330	340	349	**1019**
Included	288	296	294	**878**
Withdrawn due to	13	10	16	**39**
Medical reason	5	1	3	**9**
Non-medical reason	-	-	3	**3**
Lost to follow-up	8	9	10	**27**
Completed**	6	5	5	**16**
Ended due to study termination***	269	281	273	**823**

n: number of patients affected
**: patients that could be selected to participate in the CL3-12911-040 follow-up study (i.e. with at least one year (365 days) of study treatment)*
***: all patients who underwent joint knee replacement in both knees*
****: At the time of the premature discontinuation of the study, these patients were on-going in the study. They were thus considered with the status "ended due to study termination"*

Of the 1206 patients included in the CL3-12911-018 study with at least one year of study treatment, 878 patients were included in the present study: 288 patients in the former SrRan 1 g group, 296 patients in the former SrRan 2 g group, and 294 patients in the former placebo group. *Note: the term former refers to the treatment received by the patients during the CL3-12911-018 study, as patients did not receive any study drug during the present study.* A total of 39 patients (4.4% of the included patients) withdrew the study (4.5% in the former SrRan 1 g group, 3.4% in the former SrRan 2 g group, and 5.4% in the former placebo group). The patient's withdrawals were mainly due to patient lost to follow-up (3.1%: 2.8% in the SrRan 1 g group, 3.0% in the SrRan 2 g group, and 3.4% in the placebo group).

SUMMARY – CONCLUSIONS (Cont'd)

DISPOSITION OF PATIENTS AND ANALYSIS SETS (Cont'd)

Due to the premature study discontinuation, 16 patients (1.8% of the included patients) completed the study (*i.e.* corresponding to patients that underwent knee replacement in both knees), and 823 patients (93.7%) ended prematurely the study. The follow-up of the study lasted at maximum 24 months.

BASELINE CHARACTERISTICS

Demographic and other baseline characteristics did not show any relevant between-group differences, in the Included Set follow-up. Patients were in average 67.8 ± 7.0 years old, and most of them were aged above 65 years (60.0%). Most of the patients were women (70.4%). At inclusion in the study, 18.1% of the patients were receiving a treatment for OA: 17.0% in the SrRan 1 g group, 18.2% in the SrRan 2 g group, and 19.0% in the placebo group. These treatments were mainly Antiinflammatory and antirheumatic products (12.0%), including mostly glucosamine sulfate (7.5%). During the study, 31.4% received at least one concomitant treatment for OA (30.9%, 30.4%, and 33.0%, respectively). These treatments were mainly Antiinflammatory and antirheumatic products (20.3%) and Drugs for treatment of bone diseases (5.1%).

EFFICACY RESULTS

Evaluation criterion: knee joint replacement

A knee joint replacement was reported with a similar frequency in the three treatment groups: 26 patients, 9.0% in the SrRan 1 g group, 32 patients, 10.8% in the SrRan 2 g group, and 27 patients, 9.2% in the placebo group.

SAFETY RESULTS

The weight was the only parameter assessed during this study. No relevant between-group differences were observed for the weight at baseline (81.4 ± 14.6 kg in the SrRan 1 g group, 79.28 ± 14.39 kg in the SrRan 2 g group, and 79.0 ± 14.6 kg in the placebo group), or at post-baseline visits (M12: 80.5 ± 14.59 kg, 78.8 ± 14.8 kg, 78.4 ± 13.8 kg, respectively, M24: 80.1 ± 14.0 kg, 79.0 ± 14.8 kg, and 78.6 ± 13.9 kg, respectively).

CONCLUSION

This study was an international, multicentre 5-year follow-up study, conducted in 878 patients, with primary knee osteoarthritis, previously treated for at least one-year (with either strontium ranelate 1 g, 2 g, or placebo) during the CL3-12911-018 study. The patients did not receive any study treatment in the present study. This study, prematurely ended due to the Sponsor decision (for strategic reasons), lasted at maximum 2 years. Thus, most of the patients did not complete the study. Among the patients included in the study, the knee joint replacement was reported with similar frequency in the three former treatment groups (9.0% in the SrRan 1 g group, 10.8% in the SrRan 2 g group, and 9.2% in the placebo group).

Date of the report: 04 November 2014

Version of the report: Final version