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| *Document title* | **CLINICAL STUDY SYNOPSIS REPORT** |
| *Study title* | **A double-blind, multicenter, international randomised study to assess the effects of 4 month-oral administration of 2 g per day of strontium ranelate *versus* placebo on the bone quality and remodeling, as assessed on an alveolar bone biopsy extracted before dental implantation, in osteoporotic patients or in patients at risk of osteoporotic fracture.** |
| *Test drug code* | **Strontium Ranelate (S12911)** |
| *Indication* | **Dental implants** |
| *Development phase* | **Phase II** |
| *Protocol code* | **CL2-12911-039** |
| *Study initiation date* | **27 February 2012** |
| *Study completion date* | **24 May 2013** |
| *Main coordinator* | [redacted] **Germany** |
| *Sponsor* | **Institut de Recherches Internationales Servier (I.R.I.S.)**<br>**50 rue Carnot**<br>**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* | **25 March 2014** |
| *Version of the report* | **Final version** |

~~**CONFIDENTIAL**~~

## 2. SYNOPSIS

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

**Title of study:**
A double-blind, multicenter, international randomised study to assess the effects of 4 month-oral administration of 2 g per day of strontium ranelate *versus* placebo on the bone quality and remodeling, as assessed on an alveolar bone biopsy extracted before dental implantation, in osteoporotic patients or in patients at risk of osteoporotic fracture.
Protocol No.: CL2-12911-039
EudraCT No.: 2011-002370-23
The description of the study protocol given hereafter includes the modifications of the 4 substantial amendments to the protocol.

**International coordinator:** [redacted] (Berlin – Germany)

**Study centres:**
A multicentre study (10 centres – 4 countries) was planned. Finally, as the sponsor decided to stop prematurely the study due to a low recruitment rate, only one centre in Italy had included 2 patients when the study was prematurely discontinued.

**Publication (reference):** Not Applicable.

| **Studied period:** | **Phase of development of the study:** |
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| Study duration for the patients: 6 months.<br>Initiation date: 27 February 2012<br>Completion date: 24 May 2013 | Phase II |

**Objectives:**
The **primary objective** was to assess the effects of 4 month-treatment with strontium ranelate (2 g/day) in comparison with placebo on alveolar bone quality assessed by nanoindentation and alveolar bone turnover assessed by static and dynamic histomorphometry on alveolar bone biopsies.
The **secondary objectives** were:

- To assess the effect of 4 month-treatment with strontium ranelate on:
  - Alveolar bone microarchitecture assessed by histomorphometry and micro-computed tomography (microCT) on alveolar bone biopsies.
  - Alveolar bone texture assessed by texture analysis on retro-alveolar X-rays.
- To assess biological and clinical safety over 6 months.

In addition, data on implant stability were assessed after 6 months of treatment, during a follow-up visit.

**Methodology:**
International multicentre, double-blind, randomised exploratory, placebo-controlled Phase II study, conducted in osteoporotic patients or in patients at risk of osteoporotic fracture.

**Number of patients:**
Planned: 60 (30 patients in strontium ranelate group and 30 in placebo group).
Included: 2 (1 patient in each treatment group), due to the premature study discontinuation.

**Diagnosis and main criteria for inclusion:**
**Main selection/inclusion criteria:**
Ambulatory men or postmenopausal women (for at least 1 year) of at least 50 years of age with no upper age limit, having given their written informed consent for this study, and:

- 1: With known primary osteoporosis documented by a previous bone mass density (BMD) report or a letter from a physician.
- 2: If condition 1 was not applicable, with a ten year hip fracture risk ≥ 3% or/and a ten year risk of major osteoporotic fracture ≥ 20% assessed with the fracture risk assessment tool (FRAX®).
- 3: If conditions 1 and 2 were not applicable, having had at least one risk factor for osteoporotic fracture: age > 65 years, prevalent vertebral fracture, previous low trauma fracture, first degree family history of osteoporotic fracture, early menopause (< 40 years old), low body weight with a body mass index (BMI) < 20 kg/m$^2$, and accepting to undergo a BMD measurement by dual X-ray absorptiometry (DXA) before inclusion.
- For patients who had a DXA prescribed at selection, BMD T-score at the spine and /or hip ≤ -2.5 standard deviation (SD) or BMD T-score at the spine and /or hip ≤ -1 SD and at least one prevalent low trauma fracture at an osteoporotic site.
- And eligible for a premolar extraction followed by a dental implant placement, tooth extraction without complication and without inter-radicular septum.

**Study drug:**
One strontium ranelate 2 g sachet was administrated orally as one once a day at bedtime (preferably at least 2 hours after eating). Patients were to receive calcium 500 mg/day and vitamin D 400 IU/day as supplement at breakfast (one tablet of Calperos D3®).
In addition, demeclocycline as capsule of 150 mg was planned to be taken before the visit M4 to label the bone forming surfaces.
Batch No.: L0037624, L0042085.

**Reference product:**
One placebo sachet administered orally once a day at bedtime (preferably at least 2 hours after eating). Patients were to receive calcium 500 mg/day and vitamin D 400 IU/day as supplement at breakfast (one tablet of Calperos D3 ®). In addition, demeclocycline as capsule of 150 mg was planned to be taken before the visit M4.

**Duration of treatment:**
Active double-blind treatment period: 6 months (M0-M6).

**Criteria for evaluation:**

**Efficacy criteria**
The primary criteria planned were:

- Bone quality assessed on alveolar bone biopsy (at M4) by nanoindentation. The main analytical approach was the evaluation of the elastic modulus, hardness and dissipated energy.
- Bone turnover parameters assessed on alveolar bone biopsy (at M4) by histomorphometry with demeclocycline labelling.

**Safety criteria**

- Adverse events at each visit.
- Laboratory parameters assessed at selection, M4, and M6 visits: biochemistry (sodium, potassium, phosphorus, calcium, chloride, 25(OH)vitamin D, creatinine, creatinine clearance, Aspartate AminoTransferase/Alanine AminoTransferase, Gamma-Glutamyl Transferase, total ALKaline Phosphatase, Creatine Phosphokinase (CPK), and isoenzymes if CPK was above the upper limit of the normal reference ranges), and haematology (full blood cell count, prothrombine time, activated partial thromboplastin.
- Clinical evaluation: height (cm) at selection, weight (kg) at selection, M4, M6, sitting blood pressure (mmHg) and heart rate (beats per minute, bpm) at selection, inclusion, M4, and M6.

**Statistical methods:**
Due to the low number of included patients (n = 2), no statistical analyses were performed. Only individual data were provided.

**SUMMARY – CONCLUSIONS**

STUDY POPULATION AND OUTCOME

The sponsor decided to stop prematurely the study due to the difficulty of recruitment. At the time of the discontinuation, the target population was not reached, indeed only 4 patients were selected for the study. Among them, 2 patients were included and randomly assigned to one of the 2 treatment groups: 1 patient in the strontium ranelate group and 1 in the placebo group.

The two patients withdrew from the study for non-medical reason, before having performed the M4 visit (No. 00001 withdrew her consent and No. 00004 withdrew due to the sponsor's decision to stop prematurely the study). As a consequence, no post-baseline efficacy and safety (laboratory and vital signs) assessments were done. Of note, the bone labelling was not done.

**Demographic and other baseline characteristics**

As required in the selection/inclusion criteria of the study protocol, the two included patients had a premolar extraction at inclusion.

- Patient No. 00001 – Strontium ranelate group

This patient was a Caucasian female aged 65 years, with a body mass index (BMI) of 39.1 kg/m². She was reported as having an history of osteoporotic fracture (previous low trauma fracture at the 5th finger of the left foot). She had received a previous treatment for osteoporosis, Angelik® (progestogens and estrogens combination). Before her participation in the study, she had no primary osteoporosis documented by a previous BMD report or a letter from a physician, and she had no risk of hip or major osteoporotic fracture according to the FRAX® tool. At selection, the BMD T-score was > -2.5 without prevalent low trauma osteoporotic fracture at an osteoporotic site (only one previous low trauma fracture at the 5th finger of the left foot wrongly reported as an osteoporotic fracture). Thus, this patient did not fulfill the inclusion criteria regarding the osteoporosis diagnosis, leading to a protocol deviation reported. Her medical history other than osteoporosis included cholecystitis, diabetes mellitus, and anxiety.

This patient had a study treatment duration of 100 days.

- Patient No. 00004 – Placebo group

This patient was a Caucasian female aged 58 years, with a BMI of 18.4 kg/m². She was osteoporotic according to DXA examination performed before her participation in the study, and she was previously treated with cholecalciferol. She did not have any history of osteoporotic fracture. The patient had a medical history other than osteoporosis including: thalassemia beta, dyspepsia, appendicitis, meniscus lesion, uterine leiomyoma, and asthma.

This patient had a study treatment duration of 94 days.

EFFICACY RESULTS

No post-baseline efficacy assessment was done due to the premature study discontinuation of the patients.

SAFETY RESULTS

During the study, the patient No. 00001 in the strontium ranelate group had 2 emergent non-serious adverse events (joint effusion and gastric ulcer), and not considered as treatment-related by the investigator. None of these AEs led to treatment discontinuation. Both were recovering.

No potentially clinically significant abnormal values were observed at baseline for biochemistry or haematology parameters.

**CONCLUSION**

**This exploratory phase II study aimed to compare the effects of 4-month treatment with strontium ranelate 2g/day *versus* placebo on alveolar bone quality and turnover in men and post-menauposal women osteoporotic or at increased risk of osteoporotic fracture and candidate for dental implantation after premolar extraction.**

**Due to the difficulty to recruit patients the study was prematurely discontinued following the sponsor's decision. Only 2 patients (one in each treatment group) were included at the time of the study discontinuation. They withdrew the study while any post-baseline efficacy and safety measurements were done. No serious emergent adverse event (EAE) was reported, nor treatment-related EAE. None of the EAE led to premature treatment discontinuation.**

**Date of the report: 25 March 2014**

**Version of the report : Final version**