EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 May 2012
EMA/CHMP/313009/2012
Committee for Medicinal Products for Human Use (CHMP)

CHMP Type II variation assessment report

Invented name Protelos

Procedure No. EMEA/H/C/000560/II/0031

Marketing authorisation holder (MAH): Les Laboratoires Servier

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Les Laboratoires Servier submitted to the European Medicines Agency on 15 February 2011 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Protelos	strontium ranelate	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension of indication to include 'treatment of osteoporosis in men at increased risk of fracture'. Consequently, the MAH proposed to update sections 4.1, 4.6, 5.1 and 5.2 of the SmPC and to update the Package Leaflet accordingly.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Rapporteur: Kristina Dunder

Co-Rapporteur: Andrea Laslop

1.2. Steps taken for the assessment

Submission date:	15 February 2011
Start of procedure:	27 March 2011
Rapporteur's variation assessment report circulated on:	23 May 2011
Co-Rapporteur's variation assessment report circulated on:	23 May 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	23 June 2011
MAH's responses submitted to the CHMP on:	14 October 2011
Rapporteurs' joint assessment report on the MAH's responses circulated on:	24 November 2011
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	15 December 2011
MAH's responses submitted to the CHMP on:	23 March 2012
2nd Rapporteurs' joint assessment report on the MAH's responses circulated on:	4 May 2012
CHMP opinion:	24 May 2012

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMEA-000732-PIP01-09 on the granting of a (product-specific) waiver.

2. Scientific discussion

2.1. Introduction

Strontium ranelate, the active substance of Protelos/Osseor, comprises of two atoms of stable strontium and one molecule of ranelic acid. Strontium ranelate dissociates at the gastrointestinal level. Strontium is a cation chemically and physiologically closely related to calcium. Ranelic acid is organic, highly polar molecule without pharmacological activity. It is suggested that strontium acts through dual mechanisms of inhibition of resorption by osteoclasts and maintenance or stimulation of bone formation by osteoblasts.

Protelos/Osseor was granted a Marketing Authorisation (MA) by the European Commission on 21 September 2004 for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. Since the granting of the MA in the EU, strontium ranelate has been approved in 101 countries, and is currently marketed in 81 countries world-wide.

The pharmaceutical form of strontium ranelate is a granule for oral suspension, packaged in sachets containing 2g of drug substance to be taken once daily at bedtime. It is composed of an organic acid (ranelic acid) and of two atoms of stable strontium (active part of the molecule).

The scope of this variation is to extend the indication to include "Treatment of osteoporosis in men at increased risk of fracture". The application is based on one clinical efficacy and safety study, one pharmacokinetic/pharmacodynamic study in healthy male volunteers, one population pharmacokinetic study in males, and two nonclinical studies.

Epidemiology of osteoporosis in men

Osteoporosis in men is recognised as an epidemiologically relevant health problem. In men, like in women, osteoporosis is characterized by low bone mass, micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fractures. One out of three osteoporosis-related fractures occurs in the male population. These fractures are associated with higher age matched mortality in men than in women. Reduced bone mineral density (BMD) is a major risk factor for osteoporotic fractures in both sexes.

Several epidemiological studies, e. g. the EPOS study, have indicated that the incidence of vertebral fracture as a function of spine BMD is similar in males and females, incident vertebral fractures being more common in middle-aged and elderly women than in men due to the fact that at any age their spine bone density is lower. Low BMD, increased bone resorption and prevalent vertebral fractures are independent risk factors for increased risk of vertebral fracture in men. Hip BMD is strongly associated with risk of nonvertebral and hip fracture in older men and these associations are at least as strong as in women. Older men and those with lower BMD lose bone more rapidly, offering potential explanation for the increasing risk of fracture with advancing age.

In women the World Health Organisations' (WHO) definitions for osteopenia (<-1 SD below the mean for young healthy women) and osteoporosis (<-2.5 SD below this mean) are based on bone mineral density (BMD) data from Caucasian women, and allow to identify postmenopausal women at high risk for fracture. Although there is ongoing debate regarding diagnostic criteria, WHO criteria using sex-specific reference ranges are most commonly used. Using male cut-off criteria, the estimated prevalence of osteoporosis in men aged over 50 years is about 3% - 6%, and 38% - 47% for osteopenia, according to the data of the NHANES III study. In the MINOS French cohort, the prevalence of osteoporosis in men aged over 50 years varied from 4% to 17%, and from 31% to 48% for osteopenia.

Unlike the situation for females, only one third to half of all men with low bone mass and fractures have primary osteoporosis. The prevalence of secondary osteoporosis in men is high, approximately 50% of cases and approaches 70% in some studies, due to selection bias from specialist centres. The three major causes of secondary osteoporosis are long-term glucocorticoid treatment, hypogonadism and chronic alcohol abuse, but other causes are also important to rule out. Bone mass is well maintained during life, but following a decline in androgen and oestrogen levels, a decrease in bone mass occurs. As for women, the following factors can also influence bone loss: smoking, alcohol consumption, low calcium intake, vitamin D deficiency and inadequate level of physical exercise.

Treatment of osteoporosis in men should be based on the absolute risk of fracture. The bone mineral density measurement is a most important factor for decision about pharmacological treatment, but other factors - such as BMI, prevalent fractures, current smoking and excessive alcohol use - have to be taken into account. General preventive and lifestyle measures including adequate calcium and vitamin D intake are recommended after having ruled out or treated secondary/aggravating causes of osteoporosis. Pharmacologic therapy for osteoporosis is indicated in men with T-scores below -2.5 or below -1 with a prevalent fragility fracture. The first line treatment is an oral bisphosphonate,

alendronate and risedronate being available in this indication. More recently intravenous zoledronate as well as teriparatide have been approved in osteoporotic men at high risk of fractures.

2.2. Non-clinical aspects

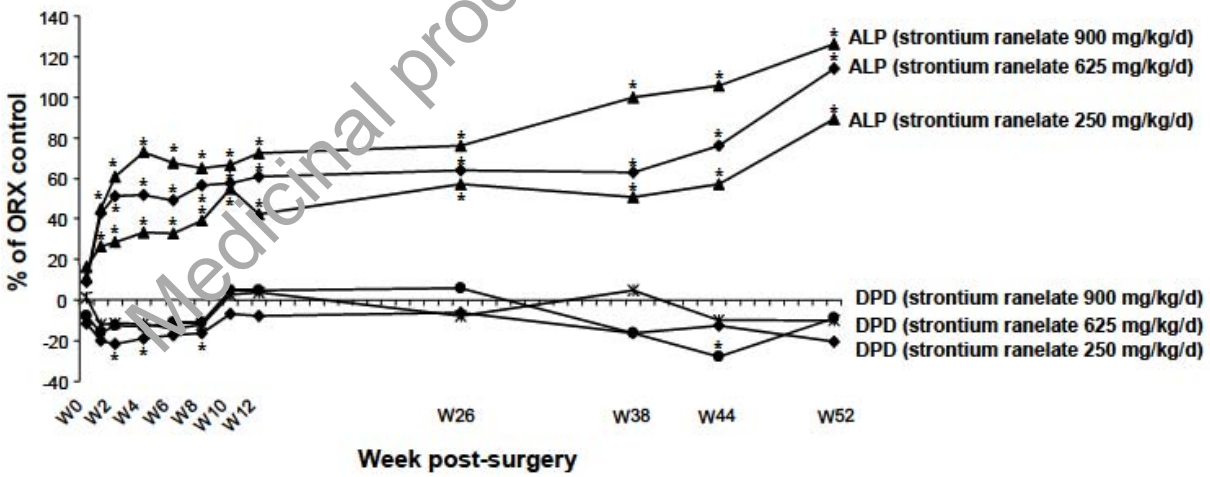
2.2.1. Methods – analysis of data submitted

Two non-clinical pharmacology studies were provided by the applicant in support of the male osteoporosis indication. The remaining preclinical safety assessment of strontium ranelate is based on the already approved product for post-menopausal osteoporosis where it also was noted that strontium ranelate did not affect mating performance or fertility in male rats.

The efficacy of strontium ranelate in male osteoporosis was assessed by long term *in vivo* studies in a pharmacological model of osteopenia (orchidectomy). The orchidectomized rat model has been considered as an animal model for androgen deficiency-induced bone loss in men. In this model, male rats were orchidectomized (ORX) and a 52-week preventive treatment was tested at oral doses ranging from 250 to 900 mg/kg/d. A curative treatment was also tested in male orchidectomized rats for 44 weeks at 625 mg/kg/day. Both studies comply with Good Laboratory Practices (GLP). Pharmacokinetic analyses were performed in both studies using bioanalytical methods with satisfactory precision and accuracy.

2.2.2. Results

The results of the preventive treatment in ORX rats have shown that strontium ranelate (250 to 900 mg/kg/d over 52 weeks) prevents orchidectomy-induced trabecular bone loss and altered trabecular microarchitecture induced by orchidectomy, by reducing ORX-induced increase in bone turn-over. This was related to a rebalance of bone turnover in favour of bone formation (sustained increase in total alkaline phosphatase (ALP) and transient decrease in deoxypyridinoline (DPD) levels). See Figure 1.



**: p<0.05 vs ORX control group. Statistics performed on actual values.*

Figure 1. Evolution of bone formation (ALP) and bone resorption (DPD) markers in ORX strontium ranelate

Treatment with strontium ranelate did not significantly prevent decreases in biomechanical strength parameters related to ORX but neither did it adversely affect any bone strength parameters. In line

with this, strontium ranelate induced no modification of the mineralization process as evaluated by osteoid thickness and mineral apposition rate (MAR). Strontium ranelate had no effect on the phosphocalcic metabolism. The exposures (AUC_{24}) to strontium were of 367, 542 and 571 mg.h/L in animals treated at 250, 625 or 900 mg/kg/d, respectively. Treatment with strontium ranelate at 250 mg/kg/day appeared slightly less efficacious than the other doses and there were generally no differences noted for the pharmacological endpoints between doses of 625 and 900 mg/kg/day, as a complete prevention of the ORX effects was noted at these dose levels.

The long-term (44 weeks) curative treatment at 625 mg/kg/day restored trabecular bone mass and microarchitecture in orchidectomized rats. As in the preventive study, this was associated with a rebalance of bone turnover in favour of bone formation (sustained increase in total alkaline phosphatase and transient decrease in deoxypyridinoline levels). Also in this study, treatment with strontium ranelate did not significantly prevent decreases in biomechanical strength parameters related to ORX. Strontium ranelate induced no modification of the mineralization process as evaluated by osteoid thickness and MAR and had no effect on the phosphocalcic metabolism. The strontium exposure in those animals treated at 625 mg/kg/d was 609 mg.h/L (AUC_{24}), comparable with the exposure obtained at the same dose after 52 weeks of preventive treatment.

Ecotoxicity/environmental risk assessment

Part III A6: Ecotoxicology

Phase I Assessment

Physico-chemical properties

Table 1: Physical and chemical properties of strontium ranelate

Parameter	Value	Units
CAS No.	5459-90-4	-
Molecular weight	513	g/mol
Water solubility (25 °C)	800	mg/L
Vapour pressure (25 °C)	to low to be measured	mPa
K_{oc}	< 18	L/kg
log K_{ow}	< -5 (pH 7.4)	-
Corrected distribution coefficient	1.47	-
pK_a	4.8 (pK_{a1}), 3.6 (pK_{a2}), 2.9 (pK_{a3}), 2.0 (pK_{a4}) and < 1.5 (pK_{a5}) In water, strontium ranelate is practically fully ionized	-
Ready biodegradability test	15% (whole period) – not readily biodegrable	-

K_{oc}… organic carbon sorption coefficient, Log K_{ow}… partition coefficient octanol/water, pK_a… acid dissociation constant

Calculation of the Predicted Environmental Concentration (PEC)

In Phase I the PEC calculation is restricted to the aquatic compartment. The following formula was used to estimate PEC in surface water ($PEC_{SURFACEWATER}$).

$PEC_{SURFACEWATER}$ = [DOSEai x Fpen] / [WasteWinhab x Dilution]

Where:

DOSEai Maximum daily dose consumed per inhabitant [mg/inh/d]

Fpen Percentage of market penetration (default value of 0.01)

WasteWinhab Amount of waste water per inhabitant per day [L/inh/d], (default value of 200)

Dilution Dilution factor (default of 10)

$PEC_{SURFACEWATER}$ Predicted environmental concentration in local surface water [mg/L]

Table 2: Input parameter used for the calculation of the $PEC_{SURFACEWATER}$

Symbol	Value	Units
DOSEai		
strontium ranelate	2000	mg/inh/d
Fpen	0.01	--
WasteWinhab	200	L/inh/d
Dilution	10	mg/L

$PEC_{SURFACEWATER}$ values were estimated to be 10 µg/L for strontium ranelate. The $PEC_{SURFACEWATER}$ for the active substance is in excess of the permissible screening value of 0.01 µg/L. Therefore a Phase II Environmental Risk Assessment (Tier A) is triggered for strontium ranelate.

Phase II Assessment Tier A – Initial Exposure Assessment

Adsorption/Desorption

Based on an adsorption/desorption study (Kühne, 2010) a K_{oc} value of < 18 L/kg was determined. The low K_{oc} value indicates that the substance strontium ranelate has a low affinity to bind to organic carbon in soil and therefore to sludge (trigger K_{OC} > 10 000 L/kg). Hence, an exposure to soil organisms and a potential risk for soil organisms (earthworms) is considered negligible.

Biodegradability

The substance strontium ranelate is not ready biodegradable in the 28 day modified Sturm test (L'Haridon, J., 2004). However, based on the results of the water sediment study (Mégel, 2011) no significant potential of the substance to shift to the sediment phase was identified. The concentration of the active substance in the sediment was less than 10 % at any time point after or at 14 days. Hence, a potential risk for sediment dwelling organisms (e.g. Chironomus riparius) is considered to be unlikely. Therefore, no Tier B risk assessment for the active substance strontium ranelate is required.

Concentration in soil

Based on an adsorption/desorption study (Kühne, 2010) a K_{OC} value of < 18 L/kg was determined. The low K_{OC} value indicates that the substance strontium ranelate has a low affinity to bind to organic

carbon in soil and thereby a potential transfer of the substance to the soil compartment is considered low.

Concentration in surface waters

The $PEC_{SURFACEWATER}$ for the intended use (2 g a.s./d) was estimated to be 10 µg/L for strontium ranelate (see Table 2).

Concentration in sediment

The water sediment study shows that the parent substance is not present at amount higher than 10% in the sediment extracts at any time interval throughout the study, thus a Tier B assessment is not necessary.

Concentration in groundwater

Entry into groundwater is considered to occur via bank filtration, except for substances with an average K_{oc} > 10 000 L/kg or for substances that are readily biodegradable or for substances that have a DT_{90} < 3 days. The substance strontium ranelate is not readily biodegradable and has a K_{oc} of < 18 L/kg. No information is given regarding the DT_{90} in water or soil compartment. Hence, the $PEC_{GROUNDWATER}$ has to be estimated according to the following formula:

$PEC_{GROUNDWATER} = 0.25 \times PEC_{SURFACEWATER}$

The $PEC_{GROUNDWATER}$ for strontium ranelate was calculated to be 2.5 µg/L.

Bioaccumulation

The log P_{OW} of the substance strontium ranelate (log P_{OW} < -5) is below the trigger of 3. Therefore, the potential risk from bioaccumulation in the aquatic food chain is considered low.

Phase II Tier A – Effect Assessment

Table 3: Summary of ecotoxicity data of the active substance strontium ranelate

Test species	Test conditions (Test duration)	EC_{50}/LC_{50}	NOEC	Reference
Fish (*Oncorhynchus mykiss*)	acute, static (96 h)	> 152 mg a.s./L	-	Manson, P., 2003
Aquatic invertebrates (*Daphnia magna*)	acute, static (48 h)	> 152 mg a.s./L	-	Manson, P., 2003
Algae (*Selenastrum capricornutum*)	chronic, static (72 h)	> 152 mg a.s./L (growth rate) > 152 mg a.s./L (biomass)	9.5 mg a.s./L (growth rate) 9.5 mg a.s./L (biomass)	Manson, P., 2003
Fish (*Brachydanio rerio*)	early life stage test (ELS), semi-static (35 d)	-	20 mg a.s./L [a]	Peither, A., 2010a
Aquatic invertebrates (*Daphnia magna*)	chronic, semi-static (21 d)	> 200 mg a.s./L	200 mg a.s./L [a]	Peither, A., 2010b [b]
Micro-organisms	Activated sludge (3 h)	> 1520 mg a.s./L	-	L'Haridon, J., 2004

[a] no significantly adverse effects at the highest test concentration

[b] The NOEC is based on effects on survival and reproduction (offspring per surviving female). Potential sub-lethal effects like length and body weight of adult daphnids were not considered. Although these parameters are not mandatory according to the OECD guideline they are recommended to be able to assess potential sub-lethal effects.

Risk assessment

Table 4: Effect assessment of the active substance strontium ranelate

Compartment	Test species	Toxicity [mg/L]	AF	PNEC [mg/L]	PEC [mg/L]	RQ	Trigger
Surface water	Algae	72 h NOEC = 9.5	10	0.95	0.01	0.01	1
Groundwater [a]	Daphnids	14 d EC_{10} = 200	10	20	0.0025	0.000125	1
Sewage treatment [b]	Activated sludge	3 h EC_{50} > 1250	100	> 12.5	0.01	< 0.8 *10^{-5}	0.1

AF…assessment factor, RQ…risk quotient (PEC / PNEC)

[a] The risk assessment for groundwater organisms is based on aquatic invertebrates (daphnids). The endpoint used for the risk assessment is based on a NOEC 0f 200 mg a.s./L derived from a study by Peither, A., 2010b. In the study sub-lethal effects (length and body weight) on adult daphnids were not considered. However, the RQ value is well below the trigger and it can be assumed that the risk for groundwater organisms is acceptable even under consideration of possible sub-lethal effects.

[a] The risk assessment for micro-organisms in activated sludge is based on an EC_{50} instead of a NOEC. Hence, an assessment factor of 100 is considered for the calculation of the $PNEC_{MICROORGANISM}$.

The calculated RQ-values are well below the trigger values indicating an acceptable risk for aquatic organisms in surface water and groundwater as well as for micro-organisms of activated sludge.

In conclusion, it is considered that the risk for aquatic organisms from exposure to the products "Osseor" and "Protelos" is acceptable according to the intended use.

No precautionary and safety measures for administration, disposal and labelling are required.

2.2.3. Discussion

The results from these non-clinical studies show that strontium ranelate has beneficial effects in the orchidectomized rat model, which is considered as an appropriate animal model for androgen deficiency-induced bone loss in men. It preserved or increased bone mass by reducing ORX-induced increases in bone turnover as shown by decreases in biochemical markers of bone turnover. The gains in bone mass and geometry parameters in rats after the treatment with 625 mg/kg/day for 44 weeks after an 8-week bone depletion period are generally comparable to animals with treatment started immediately after the orchidectomy.

The environmental risk assessment that was conducted in connection with the approval of strontium ranelate for treatment of post-menopausal osteoporosis has been updated in accordance with applicable guidelines (EMEA/CHMP/SWP/4447/00). As the product does not present a safety concern for the environment, specific wording in the product information is not considered necessary.

The proposed text for sections 4.1, 4.6, 5.1 and 5.3 in the SmPC is acceptable to the CHMP.

2.3. Clinical Pharmacology aspects

2.3.1. Methods – analysis of data submitted – and Results

Introduction

Strontium ranelate contains an organic acid (ranelic acid) and two atoms of stable, non-radioactive, strontium. The product has a dual mechanism of action, simultaneously preventing bone loss by inhibiting osteoclast resorption and increasing bone formation by inducing osteoblast formation.

The drug is administered as granules for oral suspension. The approved posology is 2 g daily at bedtime.

Due to its high polarity, the absorption, distribution and binding to plasma proteins of ranelic acid are low. There is no accumulation of ranelic acid and no evidence of metabolism in animals and humans. Absorbed ranelic acid is rapidly eliminated unchanged via the kidneys.

The absolute bioavailability of strontium is about 25% (range 19-27%) after an oral dose of 2 g and intake with calcium or food reduces the bioavailability of strontium by approximately 60-70%. Maximum plasma concentrations are reached 3-5 hours after a single dose of 2 g. Steady state is reached after 2 weeks of treatment. The effective half-life of strontium is about 60 hours. Strontium excretion occurs via the kidneys and via the gastrointestinal tract. Its plasma clearance is about 12 ml/min (CV 22%) and its renal clearance about 7 ml/min (CV 28%).

Pharmacokinetic data in male subjects has been provided from 2 studies in this application: The pharmacokinetics (PK) of strontium were assessed after single oral administration of 1g, 2g and 3g of strontium ranelate as sachet(s) of 1g at bedtime in healthy elderly male volunteers in a phase 1 study (pharmacokinetic parameters of strontium were assessed from Clinical Study Reports NP15696 and NP29996). In the phase 3 pivotal study (CL3-032), strontium exposures were evaluated after repeated oral administration of a sachet of 2g of strontium ranelate at bedtime in osteoporotic male patients, using a population PK approach and the pharmacokinetic/pharmacodynamic (PK/PD) relationship of strontium ranelate and bone mineral density (BMD) were evaluated (Clinical Study Reports NP29822 and NP29946).

Phase 1 study (Reports NP15696 and NP29996)

Eighteen healthy, Caucasian, male subjects with age ranging from 63 to 73 years (mean of 68.9±2.8 years) and with BMI between 20.1 and 33.1 kg/m² (mean of 26.6±2.9 kg/m²) were included and completed the study. The subjects received three single oral doses (1, 2 or 3 g) of strontium ranelate (1 g sachet formulation) in random order on Days 1, 29 and 57.

Blood samples were collected pre-dose up to 672 hours post dose. Urine fractions were collected from pre-dose to 48 hours post dose. Pharmacokinetic parameters of strontium and ranelic acid were analysed by a non-compartmental approach with background correction of strontium plasma concentrations and urine amount. Dose proportionality was assessed by ANOVA and if departure from proportionality was suggested from this analysis, this was further explored using the empirical power method ($y=\alpha*dose^{\beta}$).

Strontium and calcium concentrations were determined in plasma and urine by Inductively Coupled Plasma Atomic Emission Spectrometry. The method was linear from 0.0125 to 250 mg/L for strontium measurement, and from 6.25 to 500 mg/L for calcium measurement. In study sample analysis, the analytical variability of the QC standards in plasma, was always below 3.4% and the accuracy was between 88.9% and 104%. The analytical variability in urine was always below 6.0% and the accuracy was between 96.7% and 101.8%.

Ranelic acid concentrations were determined in plasma and urine by a liquid chromatographic method with tandem mass spectrometry detection. The method was linear from 2.00 to 1000 ng/mL in plasma and from 50.0 to 15000 ng/mL in urine. In study sample analysis, the analytical variability of the QC standards in plasma was below 11%, the accuracy was within 100±3%. In urine, the analytical variability was below 12.0% and the accuracy within 100±3%.

The results are shown in Table 5 and Table 6 below. Strontium exposure (Cmax and AUC) increases slightly less than in proportion to dose and this is also the case for ranelic acid. At the second and third study occasions, plasma concentrations of strontium but not ranelic acid, were measureable in pre-dose samples but at a very low level (in most cases < 0.1 mg/mL).

According to the applicant, following single oral administration of 2g of strontium ranelate in healthy elderly men, strontium AUC values (median [range]: 394 [290-683] mg.h/L) were comparable to the AUC previously obtained in post-menopausal women (median [range]: 375 [286-521] mg.h/L) when administered in the same conditions (same formulation, same dose, 3h after dinner) [Clinical Study Report NP08405].

Table 5. Strontium pharmacokinetic parameters as mean±SD (median)

Dose of S12911 (g)	1	2	3
t_{max} (h) *	5 (2, 12)	5 (3, 12)	6 (3, 12)
C_{max} (mg/L)	2.95±0.98 (2.82)	5.01±1.48 (4.58)	7.23±1.54 (7.38)
$T_{1/2}z$ (h)	168±29 (167)	153±21 (150)	152±25 (145)
AUC_{last} (mg.h/L)	229±65 (229)	399±99 (366)	589±141 (586)
AUC_{last} (µg.h/L)	-	-	-
AUC_{0-48h} (mg.h/mL)	90±28 (89)	158±41 (150)	232±49 (218)
AUC_{0-48h} (µg.h/L)	-	-	-
Ae48 (%)*	7.24 (1.8, 10.5)	4.63 (2,0, 11.9)	4.99 (1.9, 9.1)
CLr (mL/min)	4.45±2.14 (3.74)	3.80±1.52 (3.54)	3.86±1.94 (3.05)

** Median (min, max) for t_{max}, and Ae48 (%)*

Table 6. Ranelic acid pharmacokinetic parameters as mean±SD (median)

Dose of S12911 (g)	1	2	3
t_{max} (h) *	5.5 (3, 24)	6 (4, 24)	6 (4, 24)
C_{max} (mg/L)	194±155 (136)	314±158 (262)	403±142 (402)
$T_{1/2}z$ (h)	22.6±17.1 (16.2)	15.4±4.0 (15.9)	19.8±17.7 (15.2)
AUC_{last} (mg.h/L)	-	-	-
AUC_{last} (µg.h/L)	5.27±4.17 (3.53)	9.31±6.22 (6.69)	13.4±8.4 (10.5)
AUC_{0-48h} (mg.h/mL)	-		-
AUC_{0-48h} (µg.h/L)	4.33±3.36 (3.14)	7.38±4.20 (5.76)	10.4±4.8 (9.50)
Ae48 (%)*	1.69 (1.0, 6.7)	1.48 (0.81, 2.76)	1.33 (0.51, 2.89)
CLr (mL/min)	57.2±19.2 (57.6)	51.4±16.3 (52.6)	48.5±12.7 (44.7)

** Median (min, max)*

Population PK analysis

A population PK analysis for strontium levels was performed based on data collected in the pivotal Phase 3 study (Protocol CL3-12911-032) by means of non-linear mixed effects modelling (NONMEM version VI). The first-order conditional estimation (FOCE) method with INTERACTION was used. For details on the study design, please see assessment of Clinical efficacy below. Samples were collected in the morning at months 0, 3, 6, 12, 18 and 24. For this analysis data up to 12 months was used. Of 174 male subjects receiving strontium ranelate treatment, 147 subjects had at least one plasma concentration of strontium and a total of 379 concentration-time points were available for the population PK analysis. Measured concentrations with uncertainty in timing of sample were excluded from the analysis. Samples below limit of quantification were excluded.

A 1-compartment model with first-order absorption was used as a starting point based on previous knowledge. The absorption constant was fixed to a value obtained in a previous analysis in females. Inter-individual variability was estimated with exponential distribution models. A model with additive and proportional terms was evaluated for the residual error. Potential correlations between empirical Bayesian PK parameters estimates and covariates (age, body weight, body mass index (BMI), phosphoremia, calciemia, albuminemia, creatinine clearance, serum creatinine, 25OH-vitamin D,

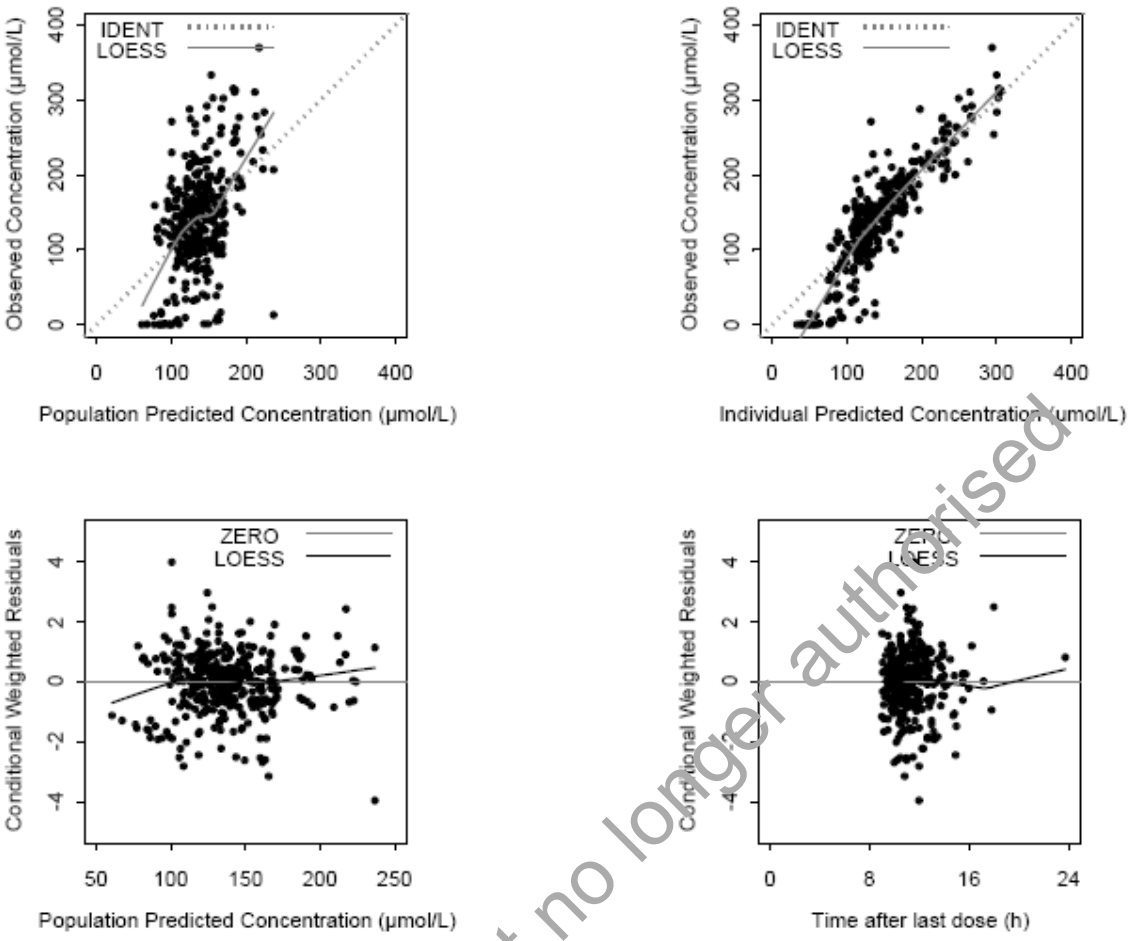
parathormone (PTH), alcohol and tobacco habits, diuretics, gastro enteric drugs) were visually inspected using graphical tools and statistical tests were performed. Shrinkage of empirical Bayes estimates of CL/F was estimated to 11%, thus the graphical exploration is reasonably adequate. The exploration suggested the following covariates on CL/F: weight, BMI, albumin, serum creatinine, creatinine clearance, phosphoremia, age, calcemia, 25OH-vitamin D and PTH levels. These were selected for a formal evaluation within the population PK model using a stepwise forward additive inclusion (alpha level of 0.05) and a backward elimination (alpha level of 0.01) approach.

During the first step of the covariate analysis, the effect of calcemia explained a significant portion of the variability of CL/F, with a marked decrease in MOF (ΔMOF= -13.61, p-value = 0.0002). During the second and third step of the covariate analysis, the effect of creatinine clearance and phosphoremia on CL/F resulted in a statistically significant decrease in MOF as well as a decrease of clearance IIV of 4.2%. No additional covariates were identified during the fourth step of the analysis. Covariates were then evaluated using a stepwise backward elimination approach (p-value <0.01). No covariate was removed from the model during the backward elimination testing.

The final model was a 1-compartment model with first order absorption and included the effect of calcemia, creatinine clearance and phosphoremia on CL/F. The parameter estimates are shown below together with goodness-of-fit plots. A visual predictive check revealed reasonable predictive properties of trough levels at 3, 6 and 12 months although variability is slightly underestimated.

Table 7. Population parameter estimates for final model

PK Parameters	Population Estimates	IIV (%)
Ka (h^{-1})	0.63, Fixed	0, Fixed
CL/F (L/h)	$2.47 \times (CA/2.3)^{3.07} \times (CRCL/3.81)^{0.477} \times (Phos/1.25)^{-0.682}$	31.9%
Vc/F (L)	75.3	0, Fixed
Additive Error (µmol/L)	37.95	



PK Figure 2. Goodness-of-fit plots for final population PK model

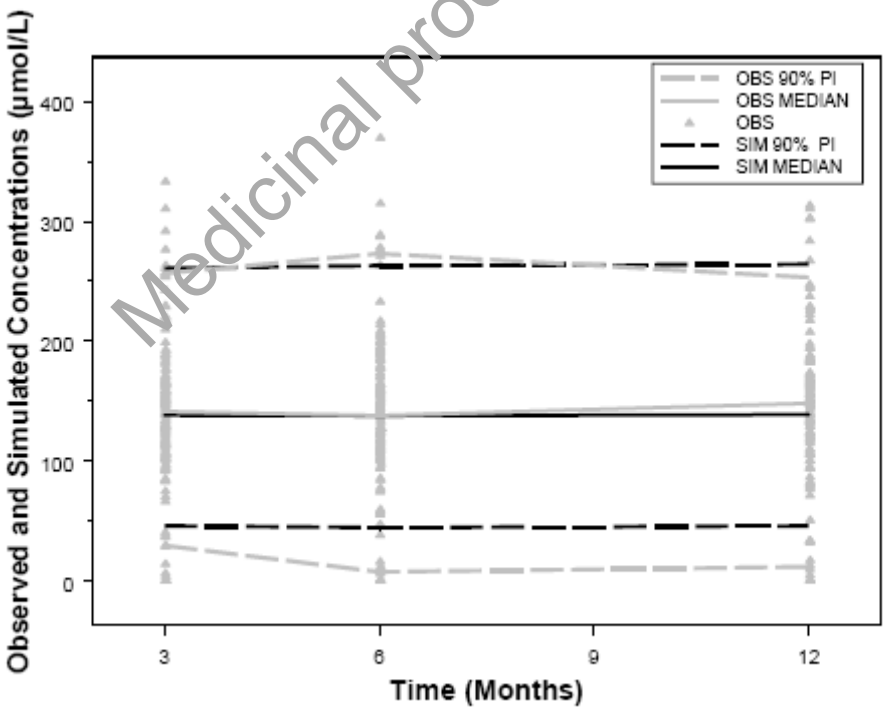


Figure 3. Visual predictive check for final population PK model

Population PKPD analysis

Based on study CL3-12911-032 (data at baseline, 3, 6 and 12 months) a population PK/PD model was developed to describe the time course of lumbar BMD L2-L4 for strontium ranelate given 2g per day on top of calcium 1000 mg and non-hydroxylated vitamin D 800 IU per day in osteoporotic men. Non-linear mixed effects modelling (NONMEM version VI) employing the first-order conditional estimation (FOCE) method with INTERACTION was used for parameter estimation. The systemic exposure used was AUC calculated using the individual empirical Bayes estimates of CL from the population PK analysis. The data set contained 258 patients (87 placebo, 171 treated), 724 observations.

The time course of BMD was described with an indirect effect model with one parameter describing bone formation (R_{FORM}) and one parameter reflecting bone resorption (K_{LOSS}). K_{LOSS} was fixed to a value reported in the literature (0.5% per year). The model assumed the effect of treatment on the formation and a baseline formation rate before treatment (R_{FORM0}), a formation rate under calcium, non-hydroxylated vitamin D and placebo (R_{FORMP}), and a formation rate under calcium, non-hydroxylated vitamin D and active treatment (R_{FORMT}) were estimated. The dependence of drug exposure on R_{FORMT} was also implemented in the model. A similar model has previously been developed on data from female patients.

The goodness-of-fit plots revealed reasonable fit to the data (not shown here). The baseline formation rate was 50% of that estimated previously in women (might be due to a different fixed K_{LOSS}). The placebo effect and treatment effect was slightly higher in men compared with that estimated in females but the placebo corrected effects were similar. The effect of systemic exposure was statistically significant. Acceptable predictive properties were demonstrated for the model (Figure 4). Simulations based on this model and the previously developed for female patients did not indicate any marked differences in the effect (Figure 5). The predicted effect of a one year strontium ranelate treatment at the 2g dose on the increase in BMD was within the same range in both populations (median [90% confidence interval], was 4.8 [4.6-4.9]% in women and 5.2 [4.1-6.3]% in men).

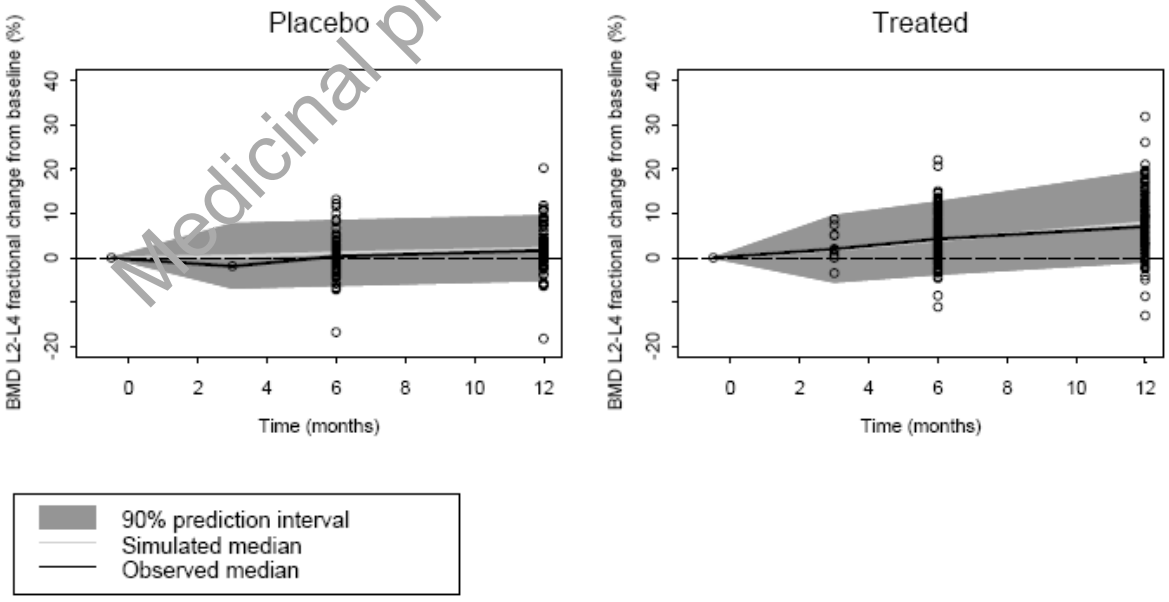


Figure 4. Visual predictive check of the population PKPD model in men

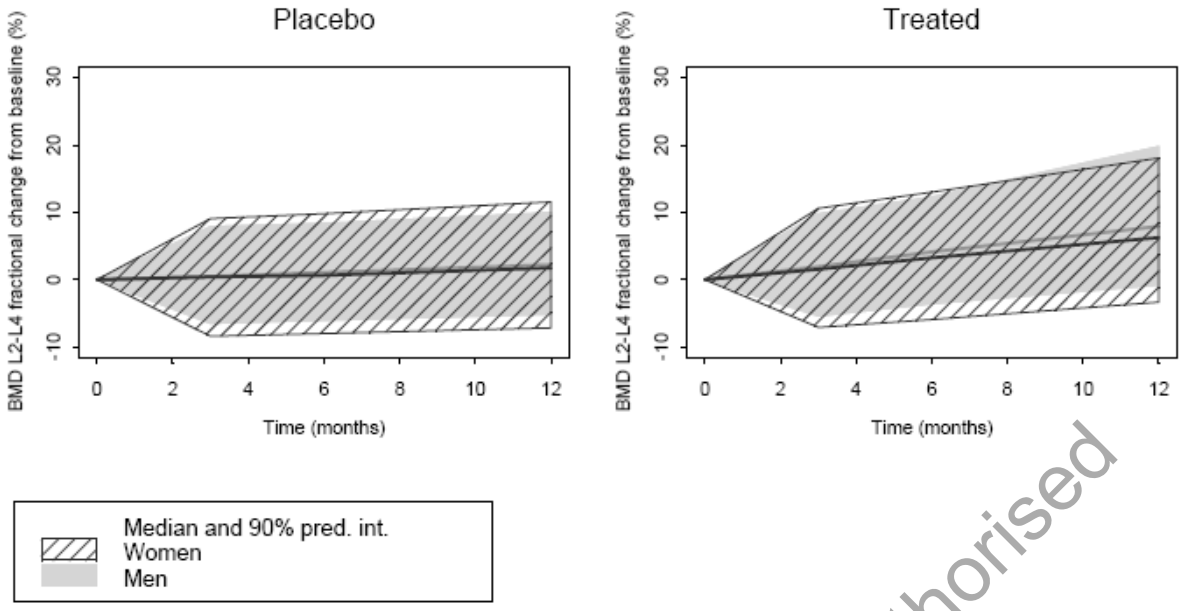


Figure 5. Comparison of the change from baseline in lumbar BMD L2-L4 in men and women through stochastic simulations

2.3.2. Discussion

Phase 1 study (Reports NP15696 and NP29996)

Pre-dose samples with measurable levels of strontium are not considered to largely impact the results.

The deviation from dose proportionality observed for strontium is in line with that observed in previous studies and has been hypothesised to be due to saturation of an active absorption process.

Comparison of the systemic exposure with that of post-menopausal females reveals similar systemic exposure although the terminal half-life estimated in this study appears to be in the upper range of previously reported mean values of half-lives (all studies range 60 to 150 hours). In addition to the study referred to by the applicant, there are two more studies available with the sachet formulation, but these studies were not performed in post-menopausal women (studies PKH-12911-002, PKH-12911-003).

Population PK analysis

The report does not completely describe the full details of the analysis. Furthermore, data below the limit of quantification were excluded and there is no description of the number of samples taken. The imprecision in model parameter estimates showed high precision for CL/F (relative standard error 4%) and acceptable precision for all parameters (RSE 20-30%) but V/F (RSE 72%), which may be expected given that only trough data are available.

From the goodness-of-fit plots it appears that low concentrations are over-predicted and the opposite for high concentrations (population predictions) possibly indicating a model misspecification or lack of identification of covariate relationships. The visual predictive check on the other hand shows reasonable predictive properties. Three covariate effects were identified and over the observed covariate range, the effect on typical CL/F is in no case more than 2-fold and dose adjustments based on these effects are not necessary.

The model is mainly used to describe the data and compare model parameters with those obtained in women. CL/F was estimated with high precision and is in agreement with that previously reported for females. In addition, the model is used for generation of AUC values for the PKPD modeling. The shrinkage of individual CL/F values were low and AUCs are therefore of good quality.

Population PKPD analysis

The model previously developed for females was not included in this submission and cannot be assessed. However, this information is not considered mandatory for approval and no questions are raised in this regard. There is no direct comparison between gender but based on the presented information and provided that the model for females is predictive, the time course of BMD L2-L4 following the same doses in females and males is in accordance and supports the dose choice in men.

Conclusion

The pharmacokinetic data indicate similar systemic exposure in osteoporotic men and postmenopausal osteoporotic women after administration of 2 g strontium ranelate/day. Further, the effects of strontium ranelate on bone turnover appear not to be gender-related. Thus, the PK/PD data provided do not suggest any differences in exposure that would necessitate a dose adjustment in the male population compared to postmenopausal females.

Overall, the pharmacokinetic documentation provided is considered sufficient and the proposed amendments to SmPC section 5.2 are acceptable to the CHMP.

2.4. Clinical Efficacy aspects

2.4.1. Methods – analysis of data submitted

The initial MAA was based on two placebo-controlled pivotal 5-year studies; the *SOTI study* and the *TROPOS study*. The granting of the initial marketing authorization was based on main analyses from these studies at 3 years of follow-up that were further completed with data obtained at 4 years, and 5 years (placebo-controlled) and further up to 10 years (open-labelled extension study). The *SOTI study* aimed to assess the efficacy in reducing vertebral fractures (1649 postmenopausal women with mean age 70 years) and the *TROPOS study* aimed to assess the efficacy in reducing non-vertebral fractures (5091 postmenopausal women with mean age 77 years). In SOTI, a significant 41% risk reduction of a new vertebral fracture *versus* placebo was evidenced over 3 years while in the TROPOS study, a 39% ($p < 0.001$) risk reductions over 3 years was seen, confirmed over 5 years with 24% ($p<0.001$) (Clinical Study Report: NP22824).

Pivotal study

The development program of strontium ranelate in male patients with osteoporosis was based on the European guideline CPMP/EWP/552/95 Rev. Nov 2006. This guideline states that once an initial marketing authorisation has been granted to a drug for the treatment of postmenopausal osteoporosis in women at high risk of fracture, a placebo-controlled study of 1 year duration with BMD as the primary endpoint could be sufficient for being granted a marketing authorization for the treatment of osteoporosis in men at increased risk of fracture, provided that: (i) the dosage used in men is justified, (ii) the included male population is at a similar fracture risk than the postmenopausal women included in the pivotal studies and (iii) the magnitude of the changes in BMD versus placebo is similar to that observed in postmenopausal osteoporotic women treated with the same compound and proportional to the decreased incidence of fractures in treated women.

Study CL3-032 (the *MALEO study*) was a prospective multicenter double-blind placebo controlled study with a treatment duration of 2 years and the main study analysis after 1 year. 54 centres in 14 countries included 261 patients in the study, from study start in December 2007 to completion at Month 12 in March 2010.

Study participants

Caucasian, ambulatory men of at least 65 years of age *and* with at least one risk factor of osteoporotic fracture (age > 75 years, prevalent vertebral fracture grade I, previous low trauma fracture, family history of osteoporotic fracture, heavy smoker > 15 cigarettes/day, known low BMD, low body weight) *and* a lumbar spine L2-L4 BMD ≤ 0.840 g/cm² (Hologic apparatus) or ≤ 0.949 g/cm² (Lunar apparatus) *and/or* femoral neck BMD ≤ 0.600 g/cm² (Hologic apparatus) or ≤ 0.743 g/cm² (Lunar apparatus) were included in the study. Inclusion criteria were chosen to obtain a male population with a similar fracture risk as the postmenopausal women included in SOTI and TROPOS. A BMD measurement had to be carried out during the selection visit and evaluation had to be done by the investigator. As incident vertebral fractures are more common in middle-aged and elderly women than in men (because at any age their spine bone density is lower), osteoporosis in average begins 10 years later in men than in women. The lower limit age was thus increased from 50 years of age in SOTI study to 65 years of age in this study.

Patients with BMD T-score below –4.0 at one or more of the measured sites *or* > 2 prevalent mild (Grade 1) and/or moderate (Grade 2) osteoporotic vertebral fractures *or* severe osteoporotic vertebral fracture (Grade 3) were excluded. Vertebral fractures were evaluated using an X-ray of the spine carried out during the selection visit. The fracture grading was based on investigator reading.

Forbidden previous treatments were glucocorticoids, antiepileptics, and drugs interfering with bone metabolism. During the study, patients with the following treatments were to be withdrawn from the study: fluoride salts, bisphosphonates, parathormone, calcitonin, other forms of vitamin D. Antacid use was not allowed within 2 hours from the timepoint of strontium ranelate administration because they decrease the absorption of the treatment. In Amendment No. 2 an item was added to prevent patients from taking quinolone and tetracycline together with strontium ranelate because strontium ranelate can decrease the absorption of antibiotics.

Table 8. Main inclusion and non inclusion criteria in the SOTI, TROPOS and CL3-032 studies

Criteria	SOTI	TROPOS	CL3-032 study
Age	≥ 50 years without upper limit	≥ 74 years without upper limit Between 70 and 74 years old if at least one additional risk factor exists*	≥ 65 years without upper limit
BMD	Lumbar BMD ≤ 0.840g/cm² (Hologic device)	Femoral Neck (FN) BMD ≤0.600 g/cm² (Hologic device)	Lumbar BMD ≤ 0.840g/cm² OR FN BMD ≤ 0.600 g/cm² (Hologic device)**
Prevalent vertebral fractures	Mandatory No limit of severity	Possible	Prevalent vertebral fractures possible but: - ≤ 2 mild (Grade 1) and/or moderate (Grade 2) fractures - No grade 3 fractures
Non authorized concomitant diseases	- Severe alcohol abuse, - Severe malabsorption, - Endocrine and skeletal diseases leading to secondary OP or osteomalacia - Spine abnormalities compromising the accurate morphometric reading of radiographs	- Severe alcohol abuse, - Severe malabsorption, - Endocrine and skeletal diseases leading to secondary OP or osteomalacia	- Severe alcohol abuse, - Severe malabsorption, - Endocrine and skeletal diseases leading to secondary OP or osteomalacia - Spine abnormalities compromising the accurate morphometric reading of DXA
Non authorized concomitant treatments	- Glucocorticoides (chronic use) - Antiepileptics used continuously - Treatments interfering with bone metabolism	- Glucocorticoides (chronic use) - Antiepileptics used continuously - Treatments interfering with bone metabolism	- Glucocorticoides (chronic use) - Antiepileptics used continuously - Treatments interfering with bone metabolism

*Personal history of osteoporotic fractures after the menopause, or resident in retirement homes, or frequent (more than 4) falls per year, or maternal history of osteoporotic fractures (hip, vertebrae, wrist).

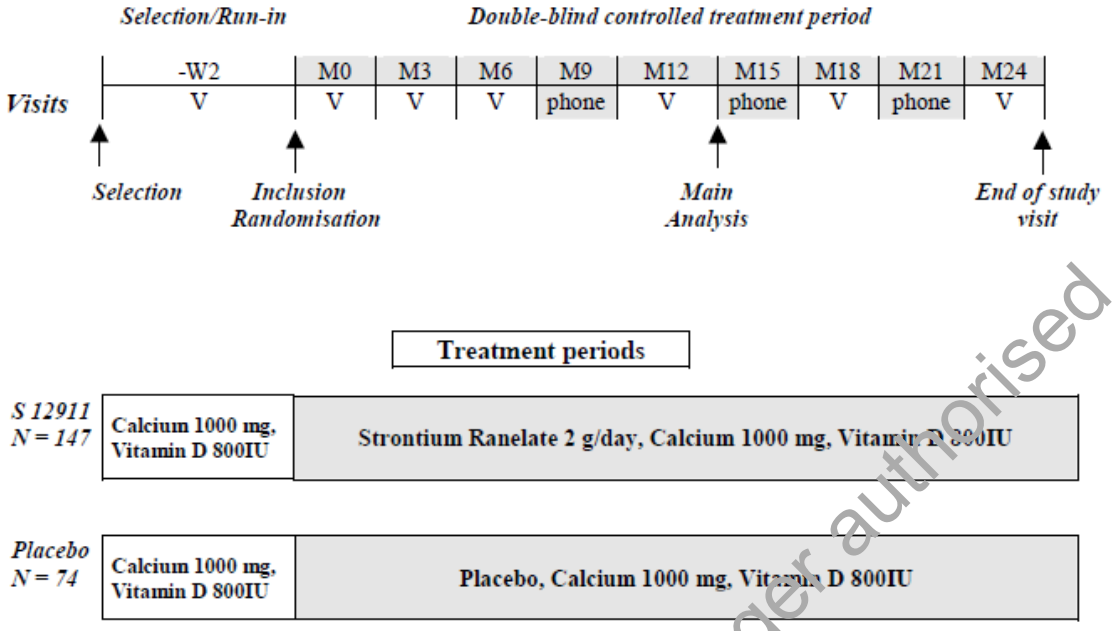
**which corresponds to Lumbar BMD ≤ 0.949 g/cm² or Femoral Neck BMD ≤0.743g/cm² (Lunar device)

Treatments

Strontium ranelate (2 g) or placebo was given orally as one sachet daily, in the evening at bedtime. Each patient in both groups received vitamin D and calcium supplements (vitamin D 800 I.U. and calcium 1000 mg) taken daily at lunchtime, for repletion of potential deficiency. The duration between selection and inclusion (run-in) was 1 to 2 weeks. The duration of treatment period was 2 years (M0 to M24). The main study analysis was done after a treatment duration of 12 months. A secondary analysis was to be done after a follow up period of another year of treatment resulting in a total treatment duration of 2 years.

Methods

Fig 6. Study plan for study CL2-032



Dose selection

In SOTI and TROPOS study, the dose of 2 g of strontium ranelate was shown to significantly reduce the risk of fractures and to increase the lumbar and femoral BMD in post-menopausal women. A similar dose was chosen in this study, since pharmacokinetics of S 12911 have been shown to be comparable in healthy elderly males and healthy post-menopausal females following a single dose of 2 g strontium ranelate (PKH-12911-012 study).

Efficacy assessments

Sample size

Sample size was estimated on the relative change in lumbar BMD from baseline to the last available post-baseline value until M12 visit. Assuming a common standard deviation of 6%, and taking into account the randomisation 2:1, 127 patients were necessary in the strontium ranelate group and 64 in placebo group (191 patients overall) to establish a statistical significant difference of at least 3% between the two groups with a power of at least 90%. Hypothesising a withdrawal rate and/or a protocol violation rate of 15%, a total of 221 patients (147 into the strontium ranelate group and 74 into the placebo group) were to be included. In fact, 261 patients were included in the study.

Randomisation

The randomisation of treatment was unbalanced with a 2/1 ratio (for ethical reasons, not to expose unnecessarily many subjects to placebo) and stratified by country.

Blinding

The investigational product and placebo granules had the same aspect (yellowish colour) and the same weight. DXA scans were analysed by an independent central reading and strontium in serum and in urine and bone markers were assessed by an independent central laboratory.

Primary objective

The main objective of this study was to demonstrate the efficacy over a 1-year period of 2 g strontium ranelate compared to placebo in men with osteoporosis on BMD at the lumbar spine (L2-L4) similar to that observed in postmenopausal women. The primary assessment was lumbar L2-L4 BMD assessed at selection visit, M6, M12, M18, and M24.

Secondary objectives were:

- To determine the efficacy of strontium ranelate over a one-year period compared to placebo in men with osteoporosis on BMD at the hip (femoral neck, total hip) and on biochemical markers of bone turnover: sCTX-I, bALP, PINP, sOC.

- To demonstrate the safety of 2 g strontium ranelate administered orally for a duration of 1 year in men.

2.4.2. Results

Disposition of patients

The different Analysis Sets were defined before study unblinding according to ICH E9 guidelines, 1998, according to the following definitions (table 9):

Table 9. Analysis sets, study CL3-032

Analysis sets		S 12911	Placebo	All
Randomised Set	**n**	**174**	**87**	**261**
Safety Set	**n (%)**	**173 (99.4)**	**87 (100.0)**	**260 (99.6)**
Efficacy Sets				
Full Analysis Set (FAS)	n (%)	161 (92.5)	82 (94.3)	243 (93.1)
Per Protocol Set (PPS)	n (%)	119 (68.4)	67 (77.0)	186 (71.3)

% :% of the Randomised Set

Table 10. Disposition of randomised patients by group, study CL3-032

Status	S 12911	Placebo	All
	n (%)	n (%)	n (%)
Included (randomised)	**174 (100.0)**	**87 (100.0)**	**261 (100.0)**
In compliance with the protocol	142 (81.6)	70 (80.5)	212 (81.2)
With a protocol deviation before or at inclusion	32 (18.4)	17 (19.5)	49 (18.8)
Withdrawn from treatment due to	*42* (24.1)*	*15 (17.2)*	*57* (21.8)*
Adverse event	24* (13.8)	9 (10.3)	33* (12.6)
Non medical Reason	14 (8.0)	6 (6.9)	20 (7.7)
Protocol deviation	4 (2.3)	-	4 (1.5)
Withdrawn from treatment but remained in the study	*8 (4.6)*	*4 (4.6)*	*12 (4.6)*
Withdrawn from the study due to	**35 (20.1)**	**11 (12.6)**	**46 (17.6)**
Adverse event	19 (10.9)	4 (4.6)	23 (8.8)
Non medical Reason	13 (7.5)	7 (8.0)	20 (7.7)
Protocol deviation	3 (1.7)	-	3 (1.1)
Lost to follow-up	-	-	-
Completed the M12 visit	**139 (79.9)**	**76 (87.4)**	**215 (82.4)**
On study treatment	*131 (75.3)*	*72 (82.8)*	*203 (77.8)*
In compliance with the protocol	127 (73.0)	72 (82.8)	199 (76.2)
With a protocol deviation after inclusion	4 (2.3)	-	4 (1.5)
Without the study treatment	*8 (4.6)*	*4 (4.6)*	*12 (4.6)*
In compliance with the protocol	-	2 (2.3)	2 (0.8)
With a protocol deviation after inclusion	8 (4.6)	2 (2.3)	10 (3.8)

**not including patient No. 032 250 0302 00041 who never took the study treatment and withdrew from the study at the M3 visit.*

Reasons for non-inclusion of selected patients (123 patients) were the following:

- Biological abnormality: 42 patients (most of them for a high level of iPTH);
- Patient's decision (mainly withdrawal of informed consent): 33 patients;
- Severe osteoporosis (one grade III, or more than two grade I or II prevalent vertebral fractures, or BMD T-score below -4.0 at one or more of the measured sites): 28 patients;
- Patients not considered as osteoporotic according to the protocol: 13 patients;
- Forbidden medical history: 5 patients;
- Forbidden medication: 1 patient;
- Other non-inclusion criteria: 1 patient.

Table 11. Disposition of randomised patients by group in the 12 month integrated analyses of efficacy (IAE) from the combined FAS dataset in SOTI and TROPOS studies

Status	S 12911	Placebo	All
	n (%)	n (%)	n (%)
Included (randomised)	**3295**	**3256**	**6551**
Withdrawn from treatment due to:	**661 (20.1)**	**565 (17.3)**	**1226 (18.7)**
Adverse event	417 (12.7)	322 (9.9)	739 (11.3)
Aggravated osteoporosis	4 (0.1)	8 (0.2)	12 (0.2)
Non medical Reason	231 (7.0)	227 (7.0)	458 (7.0)
Protocol deviation	5 (0.2)	6 (0.2)	11 (0.2)
Withdrawn from the study due to:	**469 (14.2)**	**416 (12.8)**	**885 (13.5)**
Adverse event	278 (8.4)	225 (6.9)	503 (7.7)
Aggravated osteoporosis	0 (0)	7 (0.2)	7 (0.1)
Non medical Reason	183 (5.6)	181 (5.6)	364 (5.6)
Protocol deviation	4 (0.1)	1 (0.03)	5 (0.07)
Lost to follow-up	**4 (0.1)**	**2 (0.06)**	**6 (0.09)**
Completed the M12 period	**2826 (85.8)**	**2840 (87.2)**	**5666 (86.5)**
On study treatment	*2634 (79.9)*	*2691 (82.6)*	*5325 (81.3)*
Without the study treatment	*192 (5.8)*	*149 (4.6)*	*341 (5.2)*

Study withdrawal

Treatment withdrawal: 57 patients (21.8%) prematurely stopped the study treatment; 42 patients (24.1%) in the strontium ranelate group and 15 (17.2 %) in the placebo group.

Treatment withdrawal due to adverse events: 33 patients (12.6%) prematurely stopped the treatment due to adverse events, 13.8% of patients in the strontium ranelate group (24 patients). In addition, one patient who never took the study treatment withdrew from the study at the M3 visit. 10.3% of patients in the placebo group (9 patients). One patient who never took the study treatment withdrew from the study at the M3 visit.

4 patients (2.3%) were withdrawn from the treatment due to protocol deviations in the strontium ranelate group.

After study unblinding, the following change was made to the statistical analysis plan: To study the impact of withdrawals on the main analysis, a sensitivity analysis on the relative change in lumbar L2-L4 BMD was conducted, using multiple imputation, to deal with missing data by replacing the missing information by a set of plausible values, according to the distribution of the imputed variables and covariates. Thus, missing post-baseline L2-L4 BMD values were imputed, using the information on baseline BMD and treatments group.

Moreover, a baseline carried forward analysis was also performed by the MAH.

Baseline data

Baseline data did not markedly differ between the randomised set, the full analysis set and the per protocol set.

Table 12. Main baseline characteristics at selection in the randomised set, study CL3-032

		S 12911 (N = 174)	Placebo (N = 87)	All (N = 261)
Age (years)	Mean ± SD	73.1± 6.1	72.6 ± 5.7	72.9 ± 6.0
	Min - Max	65 - 90	65 - 88	65 - 90
< 65	n (%)	-	-	-
[65 ; 75[	n (%)	112 (64.4)	59 (67.8)	171 (65.5)
[75 ; 85[	n (%)	51 (29.3)	25 (28.7)	76 (29.1)
≥ 85	n (%)	11 (6.3)	3 (3.4)	14 (5.4)
BMI (kg/m^2)	Mean ± SD	25.2 ± 3.6	26.0 ± 4.1	25.5 ± 3.7
	Min - Max	15.2 - 36.9	18.8 - 34.9	15.2 - 36.9
< 20	n (%)	9 (5.2)	4 (4.6)	13 (5.0)
[20 ; 25[	n (%)	74 (42.5)	28 (32.2)	102 (39.1)
[25 ; 30[	n (%)	74 (42.5)	39 (44.8)	113 (43.3)
≥ 30	n (%)	17 (9.8)	16 (18.4)	33 (12.6)
Time since diagnosis of osteopororosis (months)	n	174	87	261
	Mean ± SD	24.5 ± 45.3	30.8 ± 54.6	26.6 ± 48.6
	Min - Max	0 - 247	0 - 240	0 - 247
0	n (%)	68 (39.1)	31 (35.6)	99 (37.9)
]0 ; 6]	n (%)	44 (25.3)	23 (26.4)	67 (25.7)
]6 ; 12]	n (%)	5 (2.9)	4 (4.6)	9 (3.5)
]12 ; 60]	n (%)	31 (17.8)	11 (12.6)	42 (16.1)
]60 ; 120]	n (%)	15 (8.6)	9 (10.3)	24 (9.2)
> 120	n (%)	11 (6.3)	9 (10.3)	20 (7.7)
Prevalent vertebral fracture	n	173	87	260
	n (%)	50 (28.9)	22 (25.3)	72 (27.7)
Previous osteoporotic peripheral fracture	n	174	87	261
	n (%)	20 (11.5)	9 (10.3)	29 (11.1)
25(OH) vitamin D3 (nmol/L)	n	169	86	255
	Mean ± SD	64.82 ± 17.9	65.57 ± 19.42	65.07 ± 18.39

Patients had a mean age of 72.9 years, a BMI of 25.5kg/m2 and a mean T-score at the lumbar spine of -2.60. Roughly 35% of patients were older than 75years, 27.7% had a prevalent vertebral fracture and 11.1% had a prevalent osteoporotic peripheral fracture.

Current alcohol consumption was reported in 52.3% and 60.9% and current smoking by 9.2% and 14.9%, in the S12911 and placebo group, respectively. 32.2% of patients had received at least one previous treatment for osteoporosis, mainly mineral supplements (calcium, 22.6%), vitamins (vitamin D and analogues 11.5%) and bisphosphonates (11.5%).

In summary, there were no relevant differences between the S12911 arm and the placebo arm in the assessed baseline characteristics/variables.

Table 13. Comparison of main baseline characteristics in CL3-032 and the PMO population in SOTI-TROPOS IAE peripheral FAS

Baseline characteristics	Men participating in CL3-032 (N=243)	PMO women in IAE peripheral FAS (N= 6651)	Comparison
Age (years) mean (SD)	72.7 (5.7)	75.0 (6.4)	Similar
BMI (kg/m^2) mean (SD)	25.5 (3.7)	25.7 (4.1)	Similar
Lumbar spine BMD (g/cm^2) Lumbar spine T-score*	0.829 (0.113) -2.60 (1.0)	0.780 (0.151) -2.72 (1.4)	Similar
Femoral neck BMD (g/cm^2) Femoral neck T-score*	0.626 (0.086) -2.23 (0.61)	0.562 (0.075) -2.59 (0.67)	Higher in men as expected
Total hip BMD (g/cm^2) Total hip T-score*	0.794 ± 0.114 -1.58 ± 0.76	0.659 ± 0.101 -2.32 ± 0.83	
Patients with at least 1 Prevalent vertebral fracture n (%)	68 (28.0%)	2877 (48.1%)	Less prevalent fractures in male patients due to ethical considerations
Patients with at least 1 Prevalent osteoporotic fracture (any site) n(%)	87 (36.0%)	4161 (63.5%)	

*Results expressed as mean (SD) or n (%) *Hologic men and women references respectively*
*N: number of patient by treatment group - n: number of patients concerned - % (n/N)*100*

Compared with the baseline characteristics of the female population (integrated analysis of SOTI and TROPOS), male patients were of a similar age and BMI, had a slightly higher BMD at the lumbar spine, a markedly higher BMD at the femoral neck and total hip, and a lower prevalence of fractures at baseline.

Medical history: Most patients (98.5%) reported medical and/or surgical history, with no clinically relevant difference between groups. Hypertension was the most frequently reported medical history (41.8%) followed by benign prostatic hyperplasia (26.1%). Treatment groups were globally comparable in term of medical history, even if history of hypertension and of myocardial ischaemia was slightly more frequent in the strontium ranelate group than in the placebo group (43.1% *versus* 41.8% respectively and 10.3% *versus* 3.4%, respectively).

Concomitant medication: At study inclusion, most patients (84.7%) were taking at least one concomitant treatment, most frequent being antithrombotic agents, lipid modifying agents, agents acting on the renin-angiotensin system and beta-blocking agents.

Previous treatments for osteoporosis: A total of 84 patients (32.2%) reported at least one previous treatment for osteoporosis. The main previous treatments were:

- Mineral supplements (calcium): 22.6% of the patients;
- Vitamins: 12.3%, including vitamins D and analogs: 11.5%;
- Drugs for treatment of bone diseases: 11.9%, mainly bisphosphonates (11.5%).

Compliance

Table 14. Global compliance (%): Descriptive analysis in the FAS in study CL3-032

Compliance		S 12911 (N = 161)	Placebo (N = 82)	All (N = 243)
Missing	n	1	-	1
< 65%	n (%)	6 (3.8)	3 (3.7)	9 (3.7)
[65% - 80%[	n (%)	16 (10.0)	7 (8.5)	23 (9.5)
[80% - 120%[	n (%)	137 (85.6)	72 (87.8)	209 (86.4)
≥ 120%	n (%)	1 (0.6)	-	1 (0.4)
	Mean ± SD	91.3 ± 13.4	92.3 ± 10.8	91.7 ± 12.5
	Min - Max	8 - 120	49 - 106	8 - 120

Mean global compliance was higher in the PPS (94.0 ± 8.2%) as compared to the FAS but regardless of the analysis set, no relevant differences between groups were detected.

Primary efficacy results

Table 15. Lumbar L2-L4 BMD relatives changes (%) from baseline to last value in the FAS

Lumbar L2-L4 BMD (g/cm²)		S 12911 (N = 161)	Placebo (N = 82)
Baseline	Mean ± SD	0.820 ± 0.098	0.847 ± 0.136
	Min - Max	0.607 - 1.175	0.631 - 1.360
End	Mean ± SD	0.876 ± 0.106	0.860 ± 0.132
	Min - Max	0.632 - 1.230	0.641 - 1.364
Relative changes from baseline to End (%)	Mean ± SD	7.05 ± 6.00	1.72 ± 4.44
	Min - Max	-10.46 - 30.32	-17.39 - 15.54
Statistical analysis	E (SE)[1]	5.32 (0.75)	
	95%CI[2]	[3.86 ; 6.79]	
	p-value[3]	< **0.001**	

Baseline : value at selection visit ; End : last value on treatment ; (1) : Estimate (Standard Error) of adjusted means difference S 12911 - placebo (country as random effect) ; (2) : 95% Confidence Interval of the estimate ; (3) : Corresponding p-value (Student t-test, general linear model).

After one year of treatment, the relative change from baseline to End in L2-L4 BMD was 7.05 ± 6.0% in the S 12911 group and 1.72 ± 4.4% in the placebo group, with a statistically significant difference between groups (E (SE) = 5.32 (0.7)%; 95%CI = [3.9;6.8]; p<0.001).

This result was confirmed by the sensitivity analysis adjusted for risk factors (age, prevalent vertebral fractures): E (SE) = 5.33 (0.75) %, 95% CI [3.86;6.80], p<0.001.

Statistical significance in favour of strontium ranelate was achieved also in the PPS analysis set (p < 0.001).

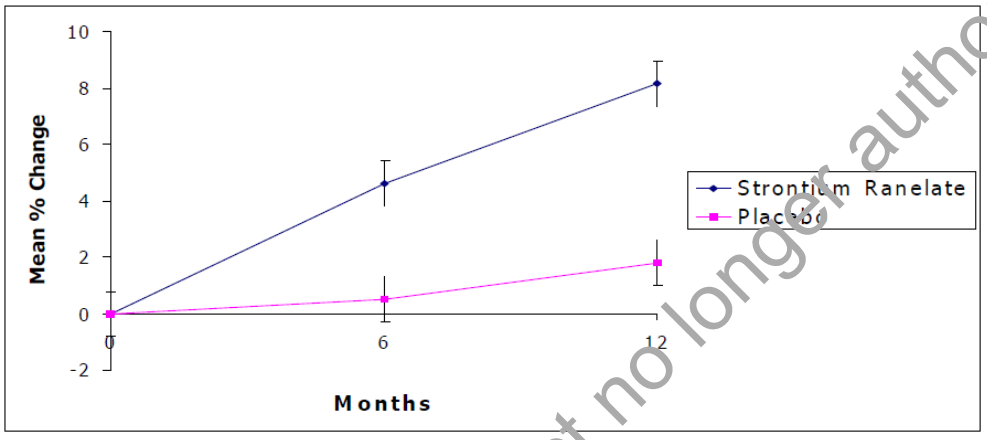
The effect size of the BMD increase at the lumbar spine for men in study CL3-032 is comparable to that observed in the female population of the SOTI and TROPOS study (integrated analysis) at 1 year: 197 men and 5175 women had available values for lumbar spine BMD at both baseline and M12 visit. The difference in mean relative increase from baseline to M12 between S 12911 and placebo was 6.38% and 7.04%, in men and in women, respectively (see table 16 below).

Table 16. L2-L4 BMD absolute and relative changes (%) from baseline to M12 as compared to placebo IAE peripheral FAS (N=6551) in SOTI + TROPOS studies

		Absolute change (g/cm^2)	Relative change (%)
M012	N	5175	5175
	E (SE)[(1)]	0.053 (0.001)	7.04 % (0.35)
	95%CI[(2)]	[0.051;0.056]	[6.70,7.38]
	p-value[(3)]	p<0.001	p<0.001

(1): Estimate of adjusted means difference S 12911-placebo (Standard Error)
(2): 95% Confidence Interval of the estimate
(3): Two sided Student t-test for independent samples / p-value is to compare with alpha=5%
N: number of patient by treatment group

Fig 7. Lumbar L2-L4 BMD relative (%) changes from baseline to M6 and M12, FAS study CL3-032



In the strontium ranelate group, the relative increases in lumbar L2-L4 BMD were 4.61 ± 4.56 % from baseline to M6 in the FAS and 8.18 ± 5.92 % from baseline to M12. During the same periods, an increase of low magnitude was observed in the placebo group: relative change from baseline to M6: 0.52 ± 4.36 % and from baseline to M12: 1.79 ± 4.55%. The difference between groups was significant at both visits: at M6: E (SE) = 4.09 (0.63)%, 95% CI = [2.85 ; 5.33], p < 0.001, and at M12: E (SE) = 6.38 (0.81)%, 95% CI = [4.78 ; 7.98], p < 0.001.

In the strontium ranelate group, the lumbar L2-L4 BMD increased by 0.037 ± 0.036 g/cm² from baseline to M6 in the FAS and by 0.066 ± 0.046 g/cm² from baseline to M12. In the placebo group, no relevant changes from baseline were detected: 0.003 ± 0.037 g/cm² at M6 and 0.013 ± 0.038 g/cm² at M12. Changes from baseline to last value were close to those observed from baseline to M12. At both visits and at last evaluation, the between-group differences in changes from baseline were significant (p < 0.001).

Missing data: Lumbar L2-L4 BMD value at M12 was missing for 46 patients (19% of the patients from the FAS). In the main analysis, the conservative approach using the last value under treatment (End) was used to deal with these missing data. To further investigate their impact on the treatment effect estimate, an analysis using the multiple imputation method was performed. The results on the relative change in lumbar L2-L4 BMD from baseline to M12 in the FAS with a multiple imputation procedure are presented in Table 17 below.

Table 17. Lumbar L2-L4 BMD relative changes (%) from baseline to M12 (multiple imputation) in the FAS (unplanned analysis in study C3-032)

Lumbar L2-L4 BMD (g/cm2)		S 12911 (N = 161)	Placebo (N = 82)
Statistical analysis	E (SE) (1)	6.25 (0.79)	
	95%CI (2)	[4.70 ; 7.80]	
	p-value (3)	**< 0.001**	

(1) Global estimate (Standard Error) after multiple imputation of the adjusted mean difference at M12 (S 12911 minus Placebo)
(2) 95% Confidence Interval of the global estimate (3) p-value of the multiple imputation test

The estimate of the between-group difference E (SE) = 6.25 (0.79)% was higher than that obtained with the main statistical approach (*i.e.* 5.32 (0.75)%), and the difference between groups was highly significant (p < 0.001). The estimate at M12 with imputation was close to the estimate obtained without imputation (*i.e.* 6.38 (0.81)%, see below), indicating that the impact of drop-outs on the estimation of the treatment effect was low.

Secondary efficacy results

Femoral neck BMD

Table 18. Femoral neck BMD changes (g/cm2) and relative changes (%) from baseline to last value in the FAS, study CL3-032

Femoral neck BMD		S 12911 (N = 161)	Placebo (N = 82)
Baseline (g/cm^2)	Mean ± SD	0.629 ± 0.082	0.629 ± 0.092
	Min - Max	0.435 - 0.892	0.470 - 0.871
End (g/cm^2)	Mean ± SD	0.648 ± 0.084	0.630 ± 0.097
	Min - Max	0.445 - 0.909	0.419 - 0.944
Changes from baseline to End (g/cm^2)	Mean ± SD	0.019 ± 0.027	0.002 ± 0.025
	Min - Max	-0.073 - 0.185	-0.058 - 0.088
Statistical analysis	E(SE)(1)	0.02 (0.00)	
	95%CI(2)	[0.01 , 0.02]	
	p-value(3)	**p < 0.001**	
Relatives changes from baseline to End (%)	Mean ± SD	3.12 ± 4.63	0.22 ± 4.05
	Min - Max	-9.06 - 34.98	-10.76 - 11.49
Statistical analysis	E(SE)(1')	2.90 (0.62)	
	95%CI(2)	[1.67 ; 4.12]	
	p-value(3)	**p < 0.001**	

Baseline : value at selection visit
End : last value on treatment
(1): Estimate (Standard Error) of adjusted means difference S 12911 – Placebo (country as random effect and femoral neck BMD at baseline as fixed effect)
(2): 95% Confidence interval of the estimate
(3): Corresponding p-value (Student t-test, general linear model)
(1') : Estimate (Standard Error) of adjusted means difference S 12911 – Placebo (country as random effect)

Total hip BMD

Table 19. Total hip BMD changes (g/cm2) and relative changes (%) from baseline to end in the FAS, study CL3-032

Total Hip BMD		S 12911 (N = 161)	Placebo (N = 82)
Baseline (g/cm^2)	Mean ± SD	0.793 ± 0.113	0.798 ± 0.117
	Min - Max	0.335 - 1.075	0.551 - 1.107
End (g/cm^2)	Mean ± SD	0.810 ± 0.111	0.801 ± 0.116
	Min - Max	0.460 - 1.113	0.550 - 1.147
Changes from baseline to End (g/cm^2)	Mean ± SD	0.018± 0.032	0.003 ± 0.020
	Min - Max	- 0.203 - 0.126	-0.071 - 0.046
Statistical analysis	E(SE)[1]	0.01 (0.00)	
	95%CI[2]	[0.01 , 0.02]	
	p-value[3]	**p < 0.001**	
Relatives changes from baseline to End (%)	Mean ± SD	2.42 ± 4.89	0.49 ± 2.47
	Min - Max	-23.74 - 37.52	-7.41 - 5.61
Statistical analysis	E(SE)[1']	1.96 (0.58)	
	95%CI[2]	[0.81 ; 3.11]	
	p-value[3]	**p < 0.001**	

(1): Estimate (Standard Error) of adjusted means difference S 12911 – Placebo (country as random effect and total hip BMD at baseline as fixed effect)
(2): 95% Confidence interval of the estimate
(3): Corresponding p-value (Student t-test, general linear model)
(1'): Estimate (Standard Error)of adjusted means difference S 12911 – Placebo (country as random effect)

A significantly greater increase in femoral neck BMD from baseline to last value was observed in the strontium ranelate group as compared with the placebo group (mean relative change 3.12 % versus 0.22%, for strontium ranelate and placebo, respectively). The absolute and relative BMD changes in the strontium ranelate group were smaller at the femoral neck than at the lumbar spine, and almost no change occurred in the placebo group at the femoral neck.

The change from baseline to last value in total hip BMD in the strontium ranelate group was small (mean relative change 2.42%), but significantly higher than in the placebo group (0.49%).

The absolute and relative changes in femoral neck BMD in men are comparable to those in the female SOTI/TROPOS population: For 178 men and 5092 women values at both baseline and M12 for femoral neck and total hip are available. The relative placebo-corrected increases in femoral neck BMD are 3.19% and 3.52%, for men and women, respectively. For total hip BMD, the relative and absolute changes in men are smaller than in women: the relative placebo-corrected increase was 1.77% in men versus 4.34% in women (see table 20 below).

Table 20. Femoral neck and total hip BMD absolute (g/cm^2) and relative changes (%) from baseline to M12 as compared to placebo IAE peripheral FAS (N=6551) in SOTI + TROPOS studies

		Absolute change (g/cm^2)	Relative change (%)
Femoral neck BMD			
M012	N	5092	5092
	E (SE)[1]	0.019 (0.001)	3.52% (0.14)
	95%CI[2]	[0.018;0.021]	[3.25;3.79]
	p-value[3]	P<0.001	P<0.001
Total hip BMD			
M012	N	5092	5092
	E (SE)[1]	0.027 (0.001)	4.34% (0.13)
	95%CI[2]	[0.026;0.029]	[4.08;4.60]
	p-value[3]	P<0.001	P<0.001

(1): Estimate of adjusted means difference S 12911-placebo (Standard Error)
(2): 95% Confidence Interval of the estimate
(3): Two sided Student t-test for independent samples / p-value is to compare with alpha=5%

Fig 8a. Femoral neck BMD relative (%) changes from baseline to Month 6 and Month 12, study CL3-032

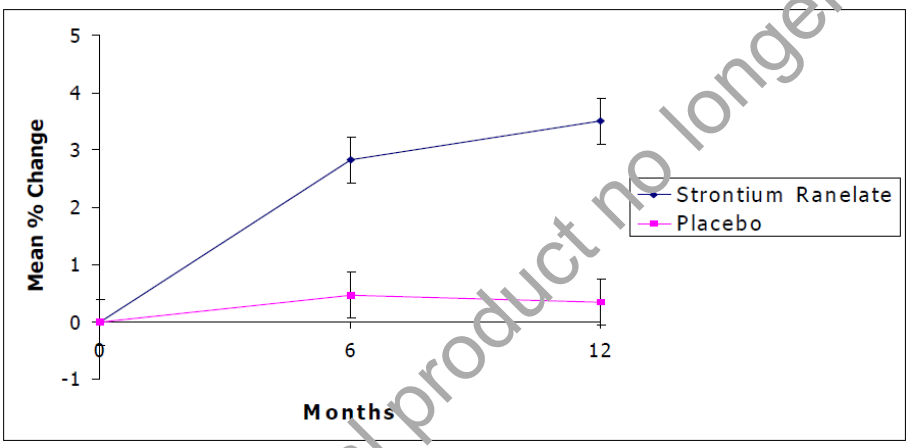
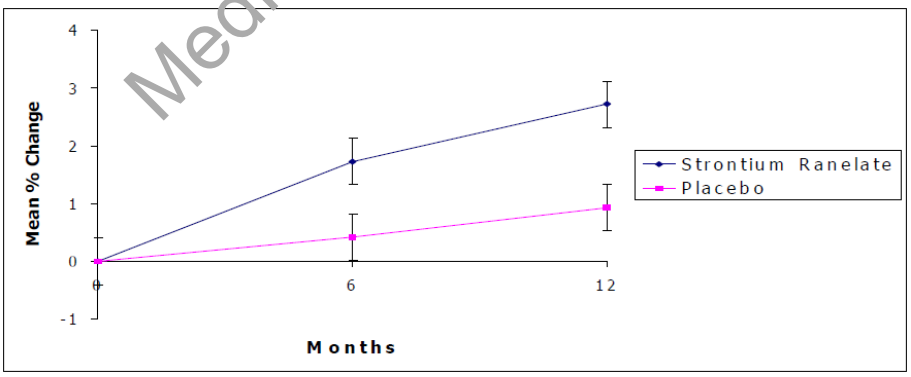


Fig 8b. Total hip BMD relative (%) changes from baseline to Month 6 and Month 12



Bone markers

Table 21. Bone markers relative changes (%) from baseline to last value in the FAS, study CL3-032

Bone markers		S 12911 (N = 161)	Placebo (N = 82)
s-CTX-I			
	n	157	79
Baseline (ng/mL)	Mean ± SD	0.47 ± 0.26	0.43 ± 0.27
	Median	0.40	0.40
	Min - Max	0.1 - 1.9	0.1 - 1.6
End (ng/mL)	Mean ± SD	0.40 ± 0.23	0.47 ± 0.27
	Median	0.40	0.40
	Min - Max	0.1 - 1.6	0.1 - 2.0
Relative change from baseline to End (%)	Mean ± SD	-4.14 ± 50.39	21.74 ± 68.27
	Min- Max	-83.3 - 300.0	-50.0 - 400.0
	E(SE)[1]	-25.88 (7.86)	
	95%CI[2]	[-41.37 ; -10.40]	
Bone alkaline phosphatase			
	n	157	79
Baseline (ng/mL)	Mean ± SD	12.96 ± 4.91	13.25 ± 4.62
	Median	12.10	12.40
	Min - Max	5.1 - 35.0	5.6 - 28.2
End (ng/mL)	Mean ± SD	12.27 ± 4.54	12.22 ± 4.43
	Median	11.40	11.30
	Min - Max	4.9 ; 37.0	5.8 ; 30.4
Relative change from baseline to End (%)	Mean ± SD	-1.69 ± 21.29	-6.07 ± 22.35
	Min - Max	-72.1 - 58.1	-34.9 - 147.2
	E(SE)[1]	4.46 (2.96)	
	95%CI[2]	[-1.37 ; 10.29]	

Baseline: Value at the inclusion vist End: last value on treatment
(1) Estimate (Standard Error) of adjusted means difference - S 12911 minus Placebo (country as random effect), using a general linear model
(2) 95% Confidence Interval of the estimate

As expected, a decrease in the levels of the bone resorption marker s-CTX (from baseline to end) was observed in the strontium ranelate group, while mean s-CTX values increased in the placebo group.

B-ALP also decreased from baseline, less markedly in the strontium ranelate group; the difference versus placebo was not significant, however.

Fig 9a. Bone formation marker B-ALP (ng/ml) over time, FAS study CL3-032

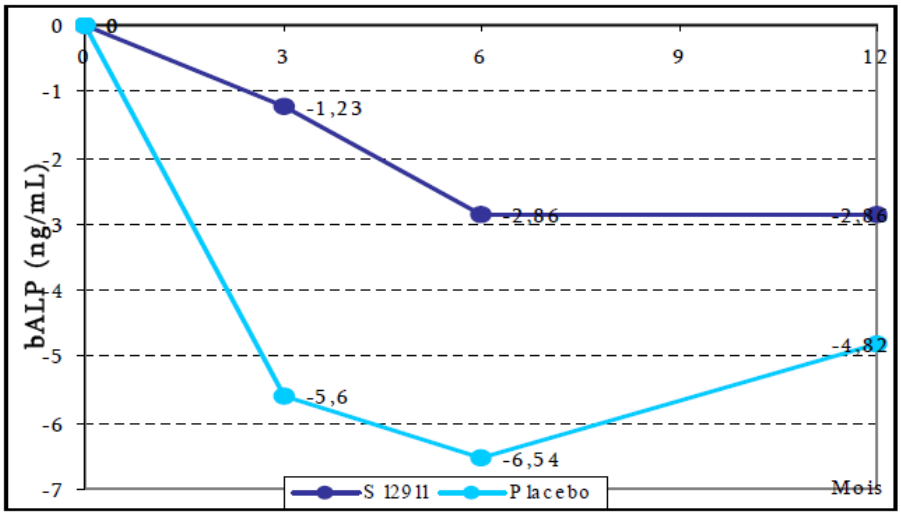
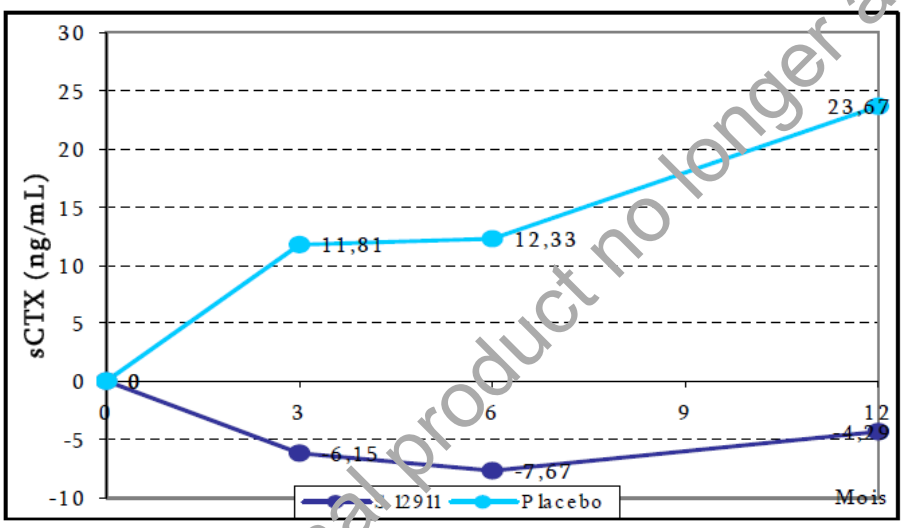


Fig 9b. Bone resorption marker s-CTX (ng/ml) over time, FAS study CL3-032



Quality of Life

Table 22. Change of mean 4-item Qualiost® score from baseline to end in the FAS, study CL3-032

		S 12911 (N = 161)	Placebo (N = 82)
Baseline	n	148	78
	Mean ± SD	1.63 ± 0.73	1.51 ± 0.60
	Min - Max	1.0 - 5.0	1.0 - 4.0
End	Mean ± SD	1.46 ± 0.67	1.43 ± 0.60
	Min - Max	1.0 - 4.5	1.0 - 3.8
Change from baseline to End	**Mean ± SD**	**-0.16 ± 0.64**	**-0.07 ± 0.48**
	Min - Max	-1.8 - 3.0	-1.2 - 2.0
	E(SE)[1]	-0.04 (0.07)	
	95%CI[2]	[-0.18 ; 0.10]	

Baseline: value at the inclusion visit; End: last value on treatment
(1): Estimate (standard-error) of adjusted mean difference S 12911 - placebo (country as random effect and baseline value as fixed effect), using a genral linear model; (2): 95% confidence interval of the estimate

The changes in quality of life were modest in both groups, with slightly greater proportions of improved patients in the strontium ranelate group vs placebo in all items.

Subgroup analyses

Not applicable.

2.4.3. Discussion

In view of the available background data from the nonclinical studies, PK study and PMO pivotal studies, the choice of dose and treatment schedules are justified. The choice of efficacy assessments parameters were reasonable and in line with those in the pivotal PMO studies. Study withdrawal rate was high, higher than calculated and higher in the strontium ranelate group than in the placebo group; and it was higher than in the pivotal PMO studies. More patients withdrew due to adverse events and to protocol violation in study CL3-032 study than in the PMO pivotal studies. The dropout rate for patients treated with strontium ranelate in the SOTI and TROPOS studies in PMO was however lower than in this study. Additional sensitivity analyses performed show that the result seems robust and is supported also with a more conservative approach, e.g. a baseline carried forward analysis, than what was initially used in the main analysis.

Lumbar L2-L4 BMD increased significantly more ($p<0.001$) months in the strontium ranelate group than in the placebo group during the 12 months observation period. The difference between treatment groups was 6.38 %, which is comparable to the difference between treatment groups at 12 months in the PMO studies (7.0 %). Femoral neck BMD as well as total hip BMD was significantly higher ($p<0.001$) in the strontium ranelate group than in the placebo group after 12 months in male study CL3-032. These differences between treatment groups are comparable to what had earlier been seen in the PMO pivotal studies for Protelos. Bone formation marker B-ALP did not significantly decrease in the strontium ranelate group during the 12 months observation period in study CL3-032 while bone resorption marker s-CTX was significantly higher in the placebo group than in the strontium ranelate group. There was a trend towards better Quality of Life in the strontium ranelate group after 12 months of treatment, however significance was reached only for sleep interfering pain.

Study CL3-032 was not powered to show any statistically significant difference between groups in terms of the reduction of vertebral fractures. Overall, the number of new fractures reported in the

study was low: After 2 years, 6 patients (3.5%) in the strontium ranelate group and 4 patients (4.6%) in the placebo group reported a non-vertebral fracture. Numerically, the incidence of morphometric vertebral fractures over 2 years was lower in the strontium ranelate (5.1%) than in the placebo group (6.9%).

According to the osteoporosis guideline (CPMP/EWP/552/95, Rev 2, 2006) the applicant should justify that the inclusion criteria chosen for the pivotal study in osteoporotic men generate a fracture risk of a similar magnitude to that of women included in the phase III pivotal studies in postmenopausal osteoporosis. for whom antifracture effect was demonstrated. Males in study CL3-032 had fewer prevalent osteoporotic fractures at baseline than females included in the PMO studies for Protelos, and more men were treated with antiosteogenic agents at baseline. The MAH argues that this is inevitable, due to ethical reasons and to development of medical praxis since the time of initiation of these female PMO studies. Males in CL3-032 are considered to be at a high risk of fracture at baseline and the male population had a pronounced vertebral osteoporosis at baseline.

It is acknowledged that it would have been difficult to include men with 2 or more prevalent fractures in a two-year placebo controlled study, given that effective treatment of osteoporotic men at high risk of fractures is available. It is also agreed that the male trial population was of sufficiently high fracture risk to justify anti-osteoporosis treatment in accordance with current treatment guidelines. Nonetheless, the fracture risk calculated with the FRAX tool clearly differs between the male and female trial populations: The 10-year probabilities of major osteoporotic fracture and of hip fracture were 10.1% and 5.4%, respectively, for men in study CL3-032, versus 24.3% and 13.0%, respectively, for women in the PMO studies.

Additional analyses comparing the treatment effect in a risk matched female and male population indicate comparable BMD increase and are considered supportive, even if comparability is shown only for the surrogate endpoint BMD and not for the fracture risk.

According to post-hoc analysis from the PMO studies, the anti-fracture efficacy of strontium ranelate was significant whatever the main determinants of vertebral fracture risks: age, baseline BMD, prevalent fractures, family history of osteoporosis, baseline body mass index (BMI), addiction to smoking and baseline level of bone turnover (Roux, 2006; Collette, 2007). Recent publications suggest that the effectiveness of strontium ranelate on clinical fractures and morphometric fractures in PMO women is comparable over the whole range of FRAX probabilities (Kanis 2011).

Given the issue of comparable fracture risk of the male and female study populations, the MAH proposes to conduct an observational cohort survey to evaluate the incidence of fractures and the adherence and tolerability of strontium ranelate in osteoporotic men treated with strontium ranelate in the post-marketing setting. The non-interventional survey is planned for 3-years and would include 3000 men with primary osteoporosis, according to sample size calculations. The MAH assumes that approximately 162 fractures would be observed during the 3-year follow up. At entry in the trial, the necessary information to calculate a 10-year fracture risk using FRAX (Kanis 2008) will be recorded.

In conclusion, BMD in lumbar spine (primary efficacy parameter) as well as secondary efficacy parameters total hip BMD and femoral neck BMD were significantly better after 12 months treatment with strontium ranelate, as compared to placebo. Results are comparable with those previously demonstrated in a female postmenopausal osteoporosis population. The proposed post-marketing study is supported and it is considered that such an observational survey could indeed yield meaningful information on the efficacy and safety of strontium ranelate treatment of male osteoporosis in clinical use.

2.5. Clinical Safety aspects

2.5.1. Methods – analysis of data submitted

The Safety Set consisted of 260 patients: 173 patients in the strontium ranelate group and 87 in the placebo group.

Table 23. Overall summary of safety results in study CL3-032 over 1 year

		S 12911 (N = 173)	Placebo (N = 87)
Patients having reported			
at least one emergent adverse event	n (%)	138 (79.8)	77 (88.5)
at least one treatment-related emergent adverse event	n (%)	40 (23.1)	23 (26.4)
Patients having experienced			
at least one serious emergent adverse event (including death)	n (%)	31 (17.9)	13 (14.9)
at least one treatment-related serious emergent adverse event	n (%)	4 (2.3)	1 (1.1)
Patients withdrawn from treatment			
due to an adverse event	n (%)	22 (12.7)	8 (9.2)
Patients who died	n (%)	2 (1.2)	1 (1.1)

Table 24. Overall summary of emergent adverse events over 2 years in CL3-032

		S 12911 (N = 173)	Placebo (N = 87)	All (N=260)
At least one EAE	**n (%)**	**153 (88.4)**	**84 (96.6)**	**237 (91.2)**
At least one treatment-related EAE	**n (%)**	**50 (28.9)**	**26 (29.9)**	**76 (29.3)**
At least one EAE leading to treatment discontinuation	**n (%)**	**31 (17.9)**	**12 (13.8)**	**43 (16.5)**
At least one serious EAE	**n (%)**	**51 (29.5)**	**26 (29.9)**	**77 (29.6)**
Treatment-related serious EAE	n (%)	6 (3.5)	2 (2.3)	8 (3.1)

EAE = Emergent Adverse Event
N : number of patients by treatment group
n : number of patients concerned
% : (n/N)*100

Patient exposure

Duration of exposure to treatment was calculated as (total treatment duration – number of days of treatment interruption). Patient exposure to the drug, as assessed by the level of serum strontium, was similar to that observed in PMO women. At Month 12, serum strontium levels were 141.5 ± 67.0µmol/L in CL3-032 *versus* 127.4 ± 67.0 µmol/L in TROPOS and 116.8 ± 77.0 µmol/L in SOTI.

Table 25. Duration of exposure to treatment in the FAS, study CL3-032

Duration (months)		S 12911 (N = 161)	Placebo (N = 82)	All (N = 243)
Missing	n	2	0	2
[0 - 3] months	n (%)	14 (8.8)	2 (2.4)	16 (6.6)
]3 - 9] months	n (%)	16 (10.1)	7 (8.5)	23 (9.5)
]9 - 11] months	n (%)	13 (8.2)	7 (8.5)	20 (8.3)
]11 - 13] months	n (%)	114 (71.7)	65 (79.3)	179 (74.3)
> 13 months	n (%)	2 (1.3)	1 (1.2)	3 (1.2)
	n	159	82	241
	Mean ± SD (days)	312.0 ± 102.5	338.3 ± 65.9	321.0 ± 92.4
	Min - Max (days)	1 - 405	9 - 404	1 - 405

Table 26. Duration of exposure to treatment in the PSS, study CL3-032

Duration (months)		S 12911 (N = 119)	Placebo (N = 67)	All (N = 186)
Missing	n	-	-	-
[0 - 9] months	n (%)	1 (0.8)	-	1 (0.5)
]9 - 11] months	n (%)	8 (6.7)	4 (6.0)	12 (6.5)
]11 - 13] months	n (%)	108 (90.8)	62 (92.5)	170 (91.4)
> 13 months	n (%)	2 (1.7)	1 (1.5)	3 (1.6)
	n	119	67	186
Mean ± SD (days)		358.6 ± 19.1	361.4 ± 14.6	359.6 ± 17.6
Min - Max (days)		268 - 405	326 - 404	268 - 405

2.5.2. Results

Adverse events during the 1-year treatment period

Table 27. Emergent adverse events reported during the 1-year treatment period, System organ classes affected in the Safety Set, study CL3-032

System organ class	S 12911 (N = 175)			Placebo (N = 87)		
	NEAE	n	%	NEAE	n	%
Gastrointestinal disorders	57	41	23.7	31	21	24.1
Musculoskeletal and connective tissue disorders	54	38	22.0	28	26	29.9
Infections and infestations	52	38	22.0	27	21	24.1
Cardiac disorders	33	21	12.1	10	9	10.3
Nervous system disorders	23	20	11.6	10	10	11.5
Skin and subcutaneous tissue disorders	22	20	11.6	11	9	10.3
Vascular disorders	20	19	11.0	9	7	8.0
Investigations	19	19	11.0	6	5	5.7
Renal and urinary disorders	16	16	9.2	10	7	8.0
Metabolism and nutrition disorders	17	13	7.5	5	5	5.7
Respiratory, thoracic and mediastinal disorders	13	11	6.4	14	13	14.9
General disorders and administration site conditions	14	11	6.4	4	4	4.6
Injury, poisoning and procedural complications	13	10	5.8	8	7	8.0
Eye disorders	11	10	5.8	4	4	4.6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10	9	5.2	4	4	4.6
Blood and lymphatic system disorders	7	6	3.5	6	6	6.9
Hepatobiliary disorders	8	6	3.5	1	1	1.1
Ear and labyrinth disorders	5	5	2.9	2	2	2.3
Reproductive system and breast disorders	5	5	2.9	-	-	-
Surgical and medical procedures	5	4	2.3	6	6	6.9
Psychiatric disorders	4	4	2.3	4	4	4.6
Endocrine disorders	-	-	-	1	1	1.1
ALL	**408**	**138**	**79.8**	**201**	**77**	**88.5**

NEAE: number of emergent adverse events
N: total number of exposed patients in the considered treatment group
n: number of patients affected
%: n/N x 100

Skin and subcutaneous disorders: This SOC was affected with an incidence of 11.6% of the patients in the strontium ranelate group *versus* 10.3% of the patients in the placebo group. Eczema was reported in 1 patient (0.6%) *versus* none, respectively. This AE occurred 10 months after the first intake of the study treatment and was not considered as related to the study treatment. The pooled incidence of rash pruritic, pruritus and generalised pruritus was close in the two groups: 9 patients (5.2%) were affected in the strontium ranelate group *versus* 4 patients (4.6%) in the placebo group. The pooled incidence for urticaria and generalised urticaria was similar in the two groups: 2 patients (1.2%) in the strontium ranelate group *versus* 1 patient (1.1%) in the placebo group. Toxic skin eruption was reported in 2 patients (1.2%) *versus* none respectively. Both events led to premature treatment discontinuation. Papular rash was reported in 1 patient (0.6%) *versus* none, respectively. Dermatitis was reported in 4 patients (4.6%) only in the placebo group: 1 case of dermatitis, 2 of allergic dermatitis and 1 of seborrhoic dermatitis. No cases of alopecia were reported.

Nervous system disorders: Headache was reported in 6 patients (3.5%) in the S 12911 group *versus* 1 (1.1%) in the placebo group. No cases of memory loss or troubles in consciousness were reported. One case of grand mal convulsion was reported in the placebo group.

Gastrointestinal disorders: Nausea was reported in 6 patients (3.5%) *versus* 2 (2.3%), respectively. Diarrhoea was reported in 7 patients (4.0%) *versus* 3 (3.4%), respectively. Abdominal pain upper was reported in 4 patients (2.3%) *versus* 2 (2.3%), respectively. Oral mucosal disorder was reported in 1 patient (0.6%) *versus* none, respectively. No cases of mouth ulceration or stomatitis were reported. No cases of loose stools were reported. One case of vomiting was reported in the placebo group.

Investigations: Transaminase increased was reported in 1 patient (0.6%) *versus* none, respectively. Hepatic enzyme increased was reported in 1 patient (0.6%) *versus* none, respectively. No cases of creatinine kinase increased were reported as adverse events.

Musculoskeletal disorders: Arthralgia was reported in 9 patients (4.6%) versus 3 (3.4%), respectively. Musculoskeletal pain was reported in 1 patient (0.6%) versus 2 (2.3%), respectively. Pain in extremity was reported in 3 patients (1.7%) versus 2 (2.3%), respectively. Muscle spasms were reported in 3 patients (1.7%) versus 2 (2.3%), respectively. Myalgia was reported in 1 patient (0.6%) versus 1 (1.1%), respectively. Bone pain was reported in 1 patient (0.6%) versus 1 (1.1%), respectively.

Vascular disorders: Deep vein thrombosis was reported in 2 patients (1.2%) *versus* none, respectively.

General disorders: Peripheral oedema was reported in 4 patients (2.3%) *versus* 1 (1.1%), respectively. Pyrexia was reported in 2 patients (2.3%) only in the placebo group.

Renal and urinary disorders: No case of interstitial nephritis was reported.

Psychiatric disorders: Depression was reported in 1 patient in each group (0.6% *versus* 1.1%, respectively). Insomnia was reported in one patient (1.1%) in the placebo group. No cases of hallucination or confusion were reported.

Respiratory, thoracic and medistinal disorders: No case of bronchial hyperactivity was reported during the study.

Fractures: A total of 5 patients experienced at least one fracture: 2 patients (1.2%) had a femoral fracture in the S 12911 group considered as not related to the study drug: 1 traumatic femur fracture (the patient fell from a bicycle) and 1 non-serious, not consolidated greater trochanter fracture diagnosed after accidental fall. 3 patients (3.4%) in the placebo group: one spinal fracture, one foot fracture and one hand fracture.

Table 28. Adverse events according to intensity during the 1-year treatment period in the Safety Set, study CL3-032

Intensity	S 12911 (N = 173)		Placebo (N = 87)	
	NEAE	%	NEAE	%
Severe	16	3.9	11	5.5
Moderate	119	29.2	51	25.4
Mild	273	66.9	139	69.2
ALL	**408**	**100.0**	**201**	**100.0**

NEAE: number of emergent adverse events ; N: total number of exposed patients in the considered treatment group ; % : NEAE by intensity/total NEAE

A total of 215 patients (82.7%) experienced at least one AE requiring either a new treatment or a surgical or medical procedure. The proportion of affected patients was lower in the strontium ranelate group: 138 patients (79.8%) than in the placebo group: 77 patients (88.5%). The AEs requiring a surgical or medical procedure were mainly related to gastrointestinal disorders: 2.9% in the strontium ranelate group *versus* 5.7% in the placebo group and cardiac disorders: 3.5% and 3.4%, respectively.

Treatment related AEs

Of all reported AEs, 40 patients (23.1%) reported 72 treatment-related emergent AEs in the strontium ranelate group and 23 patients (26.4%) reported 35 treatment-related emergent AEs in the placebo group.

AEs by outcome

Table 29. AEs by outcome during the 1-year treatment period in the Safety Set, study CL3-032

Outcome	S 12911 (N = 173)		Placebo (N = 87)	
	NEAE	%	NEAE	%
Recovery	224	54.9	119	59.2
Recovered with sequelae	1	0.2	1	0.5
Recovering/improving	50	12.3	19	9.5
Not Recovered	131	32.1	61	30.3
Fatal	2	0.5	1	0.5
All	**408**	**100.0**	**201**	**100.0**

NEAE: number of emergent adverse events
% : NEAE by outcome in a given level/total NEAE by group

Adverse events leading to treatment stopped

Table 30. AEs leading to treatment stopped during the 1-year treatment period in the Safety Set, study CL3-032

System organ/ Preferred term	S 12911 (N = 173)			Placebo (N = 87)		
	NEAE	n	%	NEAE	n	%
Gastrointestinal disorders	**8**	**6**	**3.5**	**3**	**3**	**3.4**
Dyspepsia	3	3	1.7	-	-	-
Abdominal pain upper	2	2	1.2	-	-	-
Diarrhoea	1	1	0.6	1	1	1.1
Abdominal discomfort	1	1	0.6	-	-	-
Gastroduodenitis	1	1	0.6	-	-	-
Nausea	-	-	-	1	1	1.1
Constipation	-	-	-	1	1	1.1
Skin and subcutaneous disorders	**7**	**7**	**4.0**	**1**	**1**	**1.1**
Toxic skin eruption	2	2	1.2	-	-	-
Rash pruritic	1	1	0.6	1	1	1.1
Erythema	1	1	0.6	-	-	-
Pruritus	1	1	0.6	-	-	-
Urticaria	1	1	0.6	-	-	-
Urticaria generalised	1	1	0.6	-	-	-
Nervous system disorders	**4**	**4**	**2.3**	**1**	**1**	**1.1**
Headache	3	3	1.7	-	-	-
Psychomotor hyperactivity	1	1	0.6	-	-	-
Hypersomnia	-	-	-	1	1	1.1
Vascular disorders	**3**	**3**	**1.7**	-	-	-
Deep vein thrombosis	2	2	1.2	-	-	-
Hypertension	1	1	0.6	-	-	-
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	**1**	**1**	**0.6**	**1**	**1**	**1.1**
Gastrointestinal cancer metastatic	1	1	0.6	-	-	-
Prostate cancer	-	-	-	1	1	1.1
Psychiatric disorders	**1**	**1**	**0.6**	**1**	**1**	**1.1**
Alcoholism	1	1	0.6	-	-	-
Anxiety	-	-	-	1	1	1.1
Renal and urinary disorders	**1**	**1**	**0.6**	**1**	**1**	**1.1**
Pollakiuria	-	-	-	1	1	1.1
Renal impairment	1	1	0.6	-	-	-
Cardiac disorders	**1**	**1**	**0.6**	-	-	-
Palpitations	1	1	0.6	-	-	-
Ear and labyrinth disorders	**1**	**1**	**0.6**	-	-	-
Vertigo	1	1	0.6	-	-	-
Metabolism and nutrition disorders	**1**	**1**	**0.6**	-	-	-
Anorexia	1	1	0.6	-	-	-
Musculoskeletal and connective tissue disorders	**1**	**1**	**0.6**	-	-	-
Bone pain	1	1	0.6	-	-	-
Respiratory, thoracic and mediastinal disorders	**1**	**1**	**0.6**	-	-	-
Dyspnoea	1	1	0.6	-	-	-
All	**30**	**22**	**12.7**	**8**	**8**	**9.2**

NEAE: number of emergent adverse events
N: total number of exposed patients in the considered treatment group
n: number of patients affected
%: n/N x 100

Treatment discontinuations due to AEs were more frequent within the first 3 months of treatment (45.8 % in the strontium ranelate group and 44.4 % in the placebo group).

Adverse events during the 2-year treatment period

Over the 2-year period, 91.2% of patients experienced at least one treatment emergent AE with a lower incidence in the strontium ranelate (88.4%) than in the placebo group (96.6%). The incidence of AEs leading to treatment withdrawal (mainly related to gastrointestinal disorders and skin and subcutaneous tissue disorders) was higher in the strontium ranelate group; a difference that manifested early in the study. The incidence of SAEs in the strontium ranelate (29.5%) and in the placebo (29.9%) groups were similar.

Most frequently reported emergent adverse events at 2 years

Table 31. Emergent adverse event – Analysis by System Organ Class in Safety Set (M0-M24)

System Organ class	S 12911 (N = 173)		Placebo (N = 87)	
	n	%	n	%
Musculoskeletal, connective tissue and bone disorders	52	30.1	34	39.1
Gastrointestinal disorders	52	30.1	26	29.9
Infections and infestations	51	29.5	31	35.6
Nervous system disorders	33	19.1	19	21.8
Vascular disorders	29	16.8	14	16.1
Investigations	28	16.2	13	14.9
Cardiac disorders	28	16.2	12	13.8
Skin & subcutaneous tissue disorders	25	14.5	10	11.5
Injury, poisoning and procedural complications	24	13.9	16	18.4
Renal and urinary disorders	23	13.3	10	11.5
Respiratory, thoracic and medistinal disorders	20	11.6	20	23.0
Metabolism and nutrition disorders	19	11.0	7	8.0
Blood and lymphatic system disorders	18	10.4	7	8.0
General disorders and administration site conditions	16	9.2	6	6.9
Eye disorders	14	8.1	5	5.7
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	14	8.1	10	11.5
Psychiatric disorders	9	5.2	6	6.9
Hepatobiliary disorders	8	4.6	2	2.3
Ear and labyrinth disorders	8	4.6	6	6.9
Reproductive system and breast disorders	6	3.5	0	0.0
Surgical and medical procedures	4	2.3	7	8.0
Endocrine disorders	1	0.6	2	2.3
Immune system disorders	0	0.0	1	1.1
ALL	**153**	**88.4**	**84**	**96.6**

N: number of exposed patients
n: number of patients with at least one AE under treatment in a given SOC
%: n/N x 100

The most frequently affected SOCs were musculoskeletal, connective tissue and bone disorders (30.1% in the strontium ranelate group *versus* 39.1% in the placebo group), gastrointestinal disorders (30.1% and 29.9%, respectively), infection and infestation disorders (29.5% and 35.6%, respectively). More frequently reported in the strontium ranelate group were the SOCs 'Investigations' (16.2% vs 14.9%), 'Cardiac disorders' (16.2% vs 13.8%), 'Skin and subcutaneous disorders' (14.5% vs 11.5%). The SOC vascular disorders (which showed a higher incidence in the strontium ranelate group than in the placebo group after the first year (11.0% vs 8.0%) showed by the end of the second year similar incidences in the 2 groups (16.8% vs 16.1%); this was also reflected in the incidence of hypertension (10.4 % vs 11.5%).

Table 32. Most frequently reported emergent adverse event in the strontium ranelate group in the CL3-month 0 to month 24 safety set

High level group term High level term Preferred term	S 12911 (N = 173)		Placebo (N = 87)	
	n	%	n	%
SOC investigation	**28**	**16.2**	**13**	**14.9**
+ Renal and urinary tract investigations and urinalyses	**7**	**4.0**	**4**	**4.6**
- Renal function analyses	5	2.9	1	1.1
Blood creatinine increased	5	2.9	0	0.0
Creatinine urin increased	0	0.0	1	1.1
- Urinalysis NEC	2	1.2	4	4.6
+ Physical examination topics	**7**	**4.0**	**2**	**2.3**
- Physical examination procedures	7	4.0	2	2.3
Weight increased	4	2.3	1	1.1
Weight decreased	2	1.2	1	1.1
Body temperature increased	1	0.6	0	0.0
+ Hepatobiliary investigations	5	2.9	2	2.3
- Liver function analyses	5	2.9	2	2.3
Blood bilirubin increased	1	0.6	2	2.3
Gamma-glutamytransferase increased	1	0.6	0	0.0
Hepatic enzyme increased	1	0.6	0	0.0
Liver function test abnormal	1	0.6	0	0.0
Transaminase increased	1	0.6	0	0.0
SOC cardiac disorders	**28**	**16.2**	**12**	**13.8**
+ Coronary artery disorders	**15**	**8.7**	**4**	**4.6**
- Ischaemic coronary artery disorders	11	6.4	1	1.1
Angina pectoris	7	4	0	0.0
Acute myocardial infarction	2	1.2	1	1.1
Myocardial ischaemia	2	1.2	0	0.0
Myocardial infarction	1	0.6	0	0.0
- Coronary artery disorders	7	4.0	3	3.4
Coronary artery disease	6	3.5	1	1.1
Coronary artery stenosis	1	0.6	2	2.3
+ Cardiac arrhythmias	**11**	**6.4**	**5**	**5.7**
- Supraventricular arrhytmias	5	2.9	4	4.6
- Rate and rhythm disorders	5	2.9	0	0.0
Bradychardia	3	1.7	0	0.0
Arrhytmia	1	0.6	0	0.0
Tachycardia	1	0.6	0	0.0
- Cardiac conduction disorders	3	1.7	1	1.1
- Ventricular arrhytmias and cardiac arrest	3	1.7	1	1.1
Ventricular extrasystoles	3	1.7	1	1.1
+ Heart failure	**5**	**2.9**	**2**	**2.3**
SOC Skin and subcutaneous tissue disorders	**25**	**14.5**	**10**	**11.5**
+ Epidermal and dermal conditions	**21**	**12.1**	**9**	**10.3**
- Pruritus NEC	11	6.4	7	8.0
- Dermatitis and Eczema	2	1.2	4	4.6
- Dermal and epidermal conditions NEC	4	2.3	0	0.0
Dry skin	1	0.6	0	0.0

Skin burning sensation	1	0.6	0	0.0
Transient acantholytic dermatosis	1	0.6	0	0.0
Yellow skin	1	0.6	0	0.0
- Erythemas	2	1.2	0	0.0
- Rashes, eruptions and exanthems NEC	2	1.2	0	0.0
Rash	2	1.2	0	0.0
- Bullous conditions	1	0.6	0	0.0
- Papulosquamous conditions	1	0.6	0	0.0
+ Angiodema and urticaria	3	1.7	1	1.1
- Urticarias	3	1.7	1	1.1

N: number of exposed patients
n: number of patients with at least one AE under treatment
%: n/N x 100

Regarding the *SOC investigations*, the difference between the groups over 2 years (16.2% vs 14.9%) was less than was observed at 1 year (11.0% vs 5.7%). The minor between-group differences were noted in the rates of investigations of increased blood creatinine. Among the 5 patients on strontium ranelate for whom an adverse event 'blood creatinine increased' has been reported, 3 patients had already reported an out of range value (upper threshold) at the Selection visit (127 µmol/L, 117 µmol/L and 118 µmol/L, respectively). For the 2 other patients, a mild creatinine increase was observed at M012 (<130 µmol/L) and the values were then stabilised on study treatment. These AEs were not serious and did not lead to treatment withdrawal.

The incidence of *cardiac disorders* was higher in the strontium ranelate group than in the placebo group (16.2% vs 13.8%) over 2 years, mainly due to ischaemic coronary artery disease (HLGT): angina pectoris (4% vs 0%), myocardial infarction (acute or not) (1.7% versus 1.1%) and myocardial ischemia (1.2% vs 0%). This could be explained by the higher percentage of patients in the strontium ranelate group as compared to the placebo group having a medical history of ischemic coronary artery disorder (16.1% versus 11.5%, respectively) and in particular, myocardial ischemia (10.3% versus 3.4%, respectively) and also of glucose metabolism disorders (11.0% versus 6.9%) and hypertension (42.8% versus 39.1%). The CV events were not considered treatment related by the investigators as they occurred in patients with significant cardiovascular risk factors and/or history of angina pectoris or myocardial infarction.

Over 2 years, a higher incidence of AEs in the *SOC subcutaneous and tissue disorders* was reported in the strontium ranelate group than in placebo group (14.5% vs 11.5%, respectively). This was mainly related to erythemas (1.2% vs none, respectively), rashes (1.2% versus none, respectively) and urticaria (1.7% vs 1.1%, respectively). None were serious.

Serious adverse events and deaths

Deaths

Three patients died during the study, 2 in the S 12911 group and one in the placebo group. None of the deaths were considered related to the study drug by the investigator. The cause of death was unknown for two patients (who had a heavy history of cardiac disorders) in the strontium ranelate group while one patient in the placebo group died of cerebral hemorrhage.

Serious adverse events during the 1-year treatment period

Table 33. SAEs during the 1-year treatment period in the Safety Set, study CL3-032

System organ Class	S 12911 (N = 173)			Placebo (N = 87)		
	NEAE	N	%	NEAE	N	%
Cardiac disorders	**6**	**6**	**3.5**	**4**	**4**	**4.6**
Angina pectoris	2	2	1.2	1	1	1.1
Acute myocardial infarction	1	1	0.6	1	1	1.1
Coronary artery stenosis	1	1	0.6	1	1	1.1
Bradycardia	1	1	0.6	-	-	-
Coronary artery disease	1	1	0.6	-	-	-
Left ventricular failure	-	-	-	1	1	1.1
Neoplasms benign, malignant and unspecified incl. cyst and polyps)	**4**	**4**	**2.3**	**1**	**1**	**1.1**
Prostate cancer	2	2	1.2	1	1	1.1
Gastric adenoma	1	1	0.6	-	-	-
Gastrointestinal cancer metastatic	1	1	0.6	-	-	-
Infections and infestations	**3**	**3**	**1.7**	**1**	**1**	**1.1**
Bronchiectasis	1	1	0.6	-	-	-
Lobar pneumonia	1	1	0.6	-	-	-
Pneumonia	1	1	0.6	-	-	-
Upper respiratory tract infection	-	-	-	1	1	1.1
Gastrointestinal disorders	**3**	**3**	**1.7**	-	-	-
Diverticulum intestinal haemorrhagic	1	1	0.6	-	-	-
Inguinal hernia	1	1	0.6	-	-	-
Pancreatitis	1	1	0.6	-	-	-
Musculoskeletal and connective tissue disorders	**3**	**3**	**1.7**	-	-	-
Musculoskeletal chest pain	1	1	0.6	-	-	-
Osteoarthritis	1	1	0.6	-	-	-
Spinal Osteoarthritis	1	1	0.6	-	-	-
Nervous system disorders	**2**	**2**	**1.2**	**2**	**2**	**2.3**
Encephalopathy	1	1	0.6	-	-	-
Sciatica	1	1	0.6	-	-	-
Cerebral haemorrhage	-	-	-	1	1	1.1
Grand mal convulsion	-	-	-	1	1	1.1
General disorders and administration site conditions	**2**	**2**	**1.2**	**1**	**1**	**1.1**
Death	1	1	0.6	-	-	-
Sudden death	1	1	0.6	-	-	-
Pyrexia	-	-	-	1	1	1.1
Psychiatric disorders	**2**	**2**	**1.2**	**1**	**1**	**1.1**
Alcoholism	1	1	0.6	-	-	-
Depression	1	1	0.6	-	-	-
Anxiety	-	-	-	1	1	1.1
Blood and lymphatic system disorders	**2**	**2**	**1.2**	-	-	-
Iron deficiency anaemia	2	2	1.2	-	-	-
Vascular disorders	**2**	**2**	**1.2**	-	-	-
Deep vein thrombosis	2	2	1.2	-	-	-
Surgical and medical procedure	**1**	**1**	**0.6**	**3**	**3**	**3.4**
Spinal operation	1	1	0.6	-	-	-
Aortic valve replacement	-	-	-	1	1	1.1
Nasal septal operation	-	-	-	1	1	1.1
Vitrectomy	-	-	-	1	1	1.1
Skin and subcutaneous tissue disorders	**1**	**1**	**0.6**	**1**	**1**	**1.1**
Urticaria generalised	1	1	0.6	-	-	-
Rash pruritic	-	-	-	1	1	1.1
Injury, poisoning and procedural complications	**1**	**1**	**0.6**	-	-	-
Femur fracture	1	1	0.6	-	-	-
Metabolism and nutrition disorders	**1**	**1**	**0.6**	-	-	-
Hyponatremia	1	1	0.6	-	-	-
Respiratory, thoracic and mediastinal disorders	**1**	**1**	**0.6**	-	-	-
Chronic obstructive pulmonary disease	1	1	0.6	-	-	-
All	**34**	**31***	**17.9**	**14**	**13****	**14.9**

*NAE: number of serious adverse events ; N: total number of exposed patients in the considered treatment group ; n: number of patients affected ; %: n/N x 100 ; * : Patient No 032 643 1005 00413 had chronic obstructive pulmonary disease, respiratory tract infection viral, lung abscess and pneumonia ; ** : Patient No 032 348 0505 00015 had acute myocardial infarction and cerebral haemorrhage*

Serious adverse events during the 2-year treatment period

The percentage of patients experiencing an emergent SAE in the strontium ranelate group (51 out of 173 patients: 29.5%) and in the placebo group (26 out of 87 patients: 29.9%) were similar over two years. The most frequently reported emergent SAEs in the strontium ranelate group were cardiac disorders (6.4% vs 4.6%) and gastrointestinal disorders (4.0% vs 1.1%).

Regarding the SOC 'cardiac disorders', the higher incidence of SAEs in the strontium ranelate group was mainly due to cases of myocardial ischemia, and to cardiac arrhythmia (1.2% versus none). It

might be noted that more patients reported a medical history of cardiac arrhythmia in the strontium ranelate group than in the placebo group (18.4% versus 11.5%).

Regarding the SOC 'Gastrointestinal disorders', the higher incidence of SAE in the strontium ranelate group was mainly due to cases of inguinal hernia (1.7% vs 0%). More patients reported a medical history of abdominal hernias in the strontium ranelate group than in the placebo group (23.0% versus 14.9%).

During the first year of treatment, 2 patients in the strontium ranelate group presented with a deep vein thrombosis. One 75 years old patient experienced a DVT of the right femoral vein 168 days after the first drug intake. One 66 years old patient with a history of hypercholesterolemia experienced a DVT of the left femoral vein 130 days after the first drug intake. The events were recovering in both patients when they dropped-out from the study. During the second year, one further patient in the same group experienced a suspected pulmonary embolism. This was a 78-year-old patient, with a medical history of stroke, who was hospitalised 17 months after the first study drug intake for an acute appendicitis. 7 days after surgery he experienced dyspnoea with a suspected pulmonary embolism. The study drug had been stopped at entry to hospital. The patient recovered. The event was considered by the investigator as not related to the study drug.

Comparison with PMO

Since strontium ranelate is not a hormonal treatment, no gender differences are expected in the occurrence of emergent AEs. The most frequently emergent AEs reported in the CL3-032 study (men) were compared with the frequencies reported in the PMO studies (women) after 2 years of treatment.

The randomisation (strontium ranelate: placebo) was unbalanced in CL3-032 study (with a ratio 2:1) while it was balanced in the PMO studies. It should also be noted that there was higher rate of co-morbidities in the male population with, in the men, more coronary artery disease 25.7% (versus 17.2% in the women), and more metabolism disorders 37.9% (versus 18.4% in the women) mainly related to hypercholesterolaemia 22.2% (vs 11.3%) or glucose metabolism disorders 9.6% (vs 5.1%).

Table 34. Comparison with the PMO studies of the most frequently reported emergent adverse event in Male population over 2 years

High level group term High level term Preferred term	CL3-032 study		PMO studies	
	S12911 (N=173)	Placebo (N=87)	S12911 (N=3352)	Placebo (N=3317)
	n (%)	n (%)	n (%)	n (%)
SOC Investigation	**28 (16.2)**	**13 (14.9)**	**101 (3.0)**	**106 (3.2)**
+ Renal and urinary tract investigations and urinalyses	**7 (4.0)**	**4 (4.6)**	**5 (0.1)**	**5 (0.2)**
- Renal function analyses	5 (2.9)	1 (1.1)	**1 (0.0)**	**5 (0.2)**
Blood creatinin increased	5 (2.9)	-	**1 (0.0)**	**5 (0.2)**
Creatinin urin increase	-	1 (1.1)	-	-
+ Hepatobiliary investigations	**5 (2.9)**	**2 (2.3)**	**19 (0.6)**	**19 (0.6)**
- Liver function analyses	5 (2.9)	2 (2.3)	19 (0.6)	19 (0.6)
Blood bilirubin increased	1 (0.6)	2 (2.3)	-	3 (0.1)
Gamma-glutamyl transferase increased	1 (0.6)	-	9 (0.3)	7 (0.2)
Hepatic enzyme increased	1 (0.6)	-	6 (0.2)	5 (0.2)
Liver function test abnormal	1 (0.6)	-	3 (0.1)	1 (0.0)
Transaminase increased	1 (0.6)	-	1 (0.0)	2 (0.1)
SOC cardiac disorders	**28 (16.2)**	**12 (13.8)**	**372 (11.1)**	**361 (10.9)**
+ Coronary artery disorders	**15 (8.7)**	**4 (4.6)**	**172 (5.1)**	**158 (4.8)**
- Ischaemic coronary artery disorders	11 (6.4)	1 (1.1)	149 (4.4)	142 (4.3)
Angina pectoris	7 (4)	-	101 (3.0)	102 (3.1)
Acute myocardial infarction	2 (1.2)	1 (1.1)	7 (0.2)	4 (0.1)
Myocardial ischaemia	2 (1.2)	-	25 (0.7)	25 (0.8)
Myocardial infarction	1 (0.6)	-	20 (0.6)	10 (0.3)
- Coronary artery disorders	7 (4.0)	3 (3.4)	28 (0.8)	23 (0.7)
Coronary artery disease	6 (3.5)	1 (1.1)	27 (0.8)	17 (0.5)
Coronary artery stenosis	1 (0.6)	2 (2..3)	-	-
SOC Skin and subcutaneous tissue disorder	**25 (14.5)**	**10 (11.5)**	**337 (10.1)**	**275 (8.3)**
+ Epidermal and dermal conditions	**21 (12.1)**	**9 (10.3)**	**245 (7.3)**	**189 (5.7)**
- Erythemas	2 (1.2)	-	12 (0.4)	9 (0.3)
- Rashes, eruptions and exanthems NEC	2 (1.2)	-	36 (1.1)	20 (0.6)
Rash	2 (1.2)	-	31 (0.9	13 (0.4)
+ Angiodema and urticaria	3 (1.7)	1 (1.1)	12 (0.4)	13 (0.4)
- Urticarias	3 (1.7)	1 (1.1)	10 (0.3)	12 (0.4)

N: number of exposed patients
n: number of patients with at least one AE under treatment in a given preferred term or in a given level
%: n/N x 100

The imbalance in the incidence of emergent coronary artery disorders (HLGT) reported in men (8.7% in the strontium ranelate group vs 4.6% in the placebo group) was not observed in women in the PMO studies (5.1% vs 4.8%). This could be explained by the difference in the medical histories of the populations, with in the CL3-032 study higher rates of ischemic coronary artery disorders and myocardial ischemia in particular, reported in the strontium ranelate group as compared to the placebo group (16.1% versus 11.5%, respectively, for ischemic CAD and 10.3% versus 3.4% respectively for ischemia).

AEs related to skin and subcutaneous disorders were also more frequently reported in men (14.5% vs 11.5%) than in the PMO women (10.1% vs 8.3%), probably due to the risk minimization measures set up in the Risk management plan: i.e patients are informed "to stop PROTELOS immediately and

permanently when a rash occurs and to seek medical advice." However the differences between the 2 groups in men and in PMO women were comparable.

Over 2 years, despite the higher prevalence of comorbidities in men than in women, the proportion of serious emergent AEs in the CL3-032 study was similar in the strontium ranelate group (29.5%) to the placebo group (29.9%). The most frequently reported SAEs in the strontium ranelate-treated men were coronary artery disorders (6.4% vs 4.6%) and gastrointestinal disorders (4.0% vs 1.1%) mainly explained by abdominal hernias. In the PMO studies, there were no abdominal hernias in the strontium ranelate group vs 0.1% in the placebo group.

Regarding *venous thromboembolism*, in the CL3-032 study, the annual incidence of thromboembolic events (1.06% for strontium ranelate group) is consistent with that observed in the whole male population aged of more than 65 years, based on data coming from the General Practice Research Database (GPRD) in the United Kingdom (0.96% of VTE). The incidence observed in men was slightly higher that the annual incidence observed in PMO studies (0.9% in the strontium ranelate group).

Adverse events leading to treatment discontinuation

In the CL3-032 study, the incidence of treatment withdrawals due to AE was higher in the strontium ranelate group (17.9%, 31 patients out of 173) than in the placebo group (13.8%, 12 patients out of 87). In the PMO studies, the incidence of treatment withdrawals due to AE was higher in the strontium ranelate group (18.1%) than in the placebo group (15.2%).

Table 35. Emergent adverse event leading to treatment stopped (2 years data)

	S12911 n=173	Placebo n=87
SOC Gastrointestinal disorders	**10**	**5**
Gastroduodenitis	1	0
Diarrhoea	1	1
Constipation	0	2
Flatulence	1	0
Abdominal discomfort	1	0
Nausea	0	1
Dyspepsia	1*+1**+1***	0
Abdominal pain	1+1*+1**	0
Abdominal adhesion	0	1
SOC Skin and subcutaneous tissue disorders	**7**	**1**
Urticaria	1	0
Urticaria generalised	1	0
Toxic skin eruption	2	0
Rash pruritic	1	1
Pruritus	1*	0
Erythema	1**	0
SOC nervous system disorders	**4**	**1**
Headache	2+1**	0
Hypersomnia	0	1
Psychomotor hyperactivity	1	0
SOC Vascular disorders	**3**	**1**
Deep vein thrombosis	2	0
Femoral artery occlusion	0	1
Hypertension	1	0
SOC neoplasms begnin, malignant and unspecified	**2**	**2**

(incl cysts and polyps)		
Colon cancer	0	1
Prostate cancer	1	1
Gastrointestinal cancer metastatic	1	0
SOC Infection and infestation	**2**	**0**
Appendictis	1	0
Septic schock	1	0
SOC Renal and urinary disorders	**1**	**1**
Renal impairment	1	0
Pollakiuria	0	1
SOC eye disorders	**1**	**0**
Cataract	1	0
SOC psychiatric disorders	**1**	**1**
Anxiety	0	1
Alcoholism	1	0
SOC Metabolism and nutrition disorders	**1**	**0**
Anorexia	1	0
SOC cardiac disorders	**1**	**0**
Palpitation	1***	0
SOC Musculoskletal disorders	**1**	**0**
Bone pain	1	0
SOC Respiratory, thoracic and mediastinal disorders	**1**	**0**
Dyspnoea	1***	0
SOC blood and lymphatic syst. Disorders	**1**	**0**
Leukopenia	1	0
SOC hepatobiliary disorders	**1**	**0**
Cholelithiasis	1	0
SOC general physical disoreders	**1**	**0**
General physical health deterioration	1	0
SOC Ear and labyrinth disorder	**1**	**0**
Vertigo	1*	0
ALL (patient-case)	**31 (17.9)**	**12 (13.8)**

* Patient 032-616-0904-00596: several adverse events led to treatment stopped
** Patient 032-616-0904-00328: several adverse events led to treatment stopped
*** Patient 032-616-0904-00356: several adverse events led to treatment stopped
Due to additional information obtained after M12 visit, some slight discrepancies might be noted between the 2.7.4 summary submitted(first year data) and the above data.

In addition, in the strontium ranelate group two 'sudden deaths' occurred in patients who had a heavy history of cardiac disorders. Over 2 years of treatment 17.9% of patients in the strontium ranelate group experienced an AE which led to treatment discontinuation compared to 14.8% in placebo group. The between-group difference after 2 years of treatment (3.5%) was the same as after 1 year of treatment. Already apparent within the first 6 months of the trial, the between-group difference is largely explained by discontinuations due to events concerning gastro-intestinal disorders or skin and subcutaneous disorders.

Laboratory findings

No clinically relevant changes over time or differences between groups were detected. Mean CPK value increased from baseline to end in the strontium ranelate group (mean ± SD: from 106.3 ± 57.1 IU/L to 125.5 ± 68.9 IU/L), whereas it remained stable in the placebo group (from 103.6 ± 56.5 IU/L to 105.6 ± 58.5 IU/L). There was no potentially clinically significant abnormal value in the strontium ranelate group (i.e. no values > 3 ULN) and there was no relevant between-group difference in the proportion of patients with a value above the upper limit of the normal range (6 patients, 3.8%, in the strontium ranelate group *versus* 4 patients, 4.9%, in the placebo group). There was a trend to a decrease in blood calcium (-0.06 ± 0.09 mmol/L) and to an increase in blood phosphorus (+0.15 ± 0.16 mmol/L) in the strontium ranelate group. These changes in phosphocalcic homeostasis

parameters probably related to the mechanism of action of strontium ranelate were observed in previous studies. Neither clinically relevant changes nor differences between groups over time were detected for haematological parameters.

In the Safety Set, emergent out-of reference value values were more frequently reported in the strontium ranelate group than in the placebo group for the following biochemical parameters:

- Low calcemia: 52 patients (33.1%) and 4 patients (4.9%), respectively.

- High value of serum phosphorus: 22 patients (14.0%) and 1 patients (1.2%), respectively).

- High creatininaemia: 16 patients (11.4%) in the S 12911 group *versus* 4 patients (5.5%) in the placebo group. None of these high creatinine values was potentially clinically significant (> 180 µmol/L). For these patients, no specific change regarding creatinine clearance was observed.

Electrocardiograms: No relevant between-group differences were detected. No relevant increase in mean corrected QT interval was observed in S 12911 treated patients, whatever the correction formula used.

Safety in special populations

Not applicable.

2.5.3. Discussion

The safety in men with primary osteoporosis observed in the phase III study was broadly similar to that described in women with postmenopausal osteoporosis, although long-term safety data are missing.

Twenty-four months of follow-up data showed that the total incidence of AEs over 2 years was lower in the strontium ranelate group than in the placebo group (88.4 versus 96.6 %), although the incidence of SAEs was similar between groups (29.5 % in the strontium ranelate group and 29.9 % in the placebo group). In particular, adverse events of coronary heart disorders, and skin and subcutaneous tissue disorders were more common in the strontium ranelate group than in the control group. The most frequently reported SAE in the strontium ranelate group were cardiac disorders and gastrointestinal disorders (6.1 % and 4.6 %; 4.0 % and 1.1 %).

During the first year of treatment, 2 patients in the strontium ranelate group had an SAE of deep vein thrombosis, none in the placebo group. During the second year, a patient in the strontium ranelate group suffered a suspected pulmonary embolism. Although the rate of venous thromboembolism in the male study does not exceed that of the general population of the same age, it is striking that all cases of venous thromboembolim were seen in the strontium ranelate treatment arm. Also, a greater risk of skin disorders with strontium ranelate than with placebo was confirmed. These findings are expected and the SmPC and RMP were updated with reference to these safety concerns as part of the recent Art. 20 referral procedure.

It is noted that the males in the CL3-032 study had more baseline co-morbidities than the females in the PMO studies. The fact that renal and urinary tract investigations and urinanalyses were more common in the male than in the female study population can probably be attributed to the common occurrence of benign prostate hyperplasia in elderly males. The incidence of hepatobiliary investigations was also higher in the male study population (2.9 % in the strontium ranelate group, versus 0.6 % in the corresponding female study population). Coronary artery disorders and skin and subcutaneous tissue disorders were also more common among strontium ranelate treated males than

among the corresponding group of females in the PMO studies. These differences may be due to higher baseline morbidity in the male study population as claimed by the MAH.

Myocardial ischemia was more common in the strontium ranelate group (1.2 versus 0 %). In study CL3-032, more patients in the strontium ranelate group had a history of cardiac arrhythmia. This difference in incidence of cardiac events was not seen in the PMO studies.

A higher percentage of patients in the strontium ranelate group as compared to the placebo group had a medical history of ischaemic coronary artery disease (16.2% versus 11.5%, respectively), in particular, myocardial ischaemia (10.4% versus 3.4%, respectively), glucose metabolism disorders (11.0% versus 6.9%) and hypertension (42.8% versus 39.1%). Thus, the rate of relevant co-morbidities was unbalanced between the treatment groups. However, it is acknowledged that the trial was not designed to assess cardiovascular safety.

The relative risk of ischaemic heart disease in the strontium ranelate group compared to placebo was not significantly increased in neither of the trials, with an adjusted hazard ratio of 1.24 [0.49;3.17] in the CL3-032 study, 1.13 [0.95;1.34] and 0.83 [0.58;1.18] in the TROPOS and SOTI studies, respectively. Considering the difficulties in the interpretation of these findings, the RMP has been updated with the addition of cardiac events as missing information. Further, the MAH has proposed to perform a specific study in osteoporotic patients to further assess the risk of ischaemic cardiac events, using the GPRD database. This observational retrospective study will use a population-based cohort to assess the risk of ischemic cardiac events, and a nested case-control study to investigate the potential association with strontium ranelate. Multivariate analyses taking into account risk and confounding factors will be implemented. This proposal is endorsed by the CHMP.

Due to the safety concerns discussed above, the new indication in men and the lack of long-term safety data in this population, the MAH should continue to submit 6 monthly PSURs instead of yearly PSURs, unless otherwise notified by the CHMP. Annex II and the RMP have been updated accordingly to reflect this request.

2.6. Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure, which included a risk minimisation plan.

Table 36. Summary of the risk management plan (including the changes related to the application presented *highlighted*)

Safety concern	Current pharmacovigilance activities (routine and additional)	Current risk minimisation activities (routine and additional)
Identified risks		
Hypersensitivity reactions	**In all patients experiencing a severe hypersensitivity reaction:** careful monitoring of these events in ongoing and planned strontium ranelate studies using specific questionnaires, as well as in post-marketing experience. All PSURs focus on this issue and analysis of cases are collected whatever the source submission of all cases to a group of independant experts	Information included in section 4.4 and 4.8 of the SmPC Information on DRESS is available on Servier.com website in the section FAQ (frequent asked questions) for PROTELOS Internal training Publications and communications on DRESS

	in order to assess the diagnosis of DRESS and the relationship to PROTELOS **In all patients experiencing severe hypersensitivity reaction type DRESS, TEN or SJS, practitioners in charge of them receive from MAH a letter in which they are strongly recommended to organize and perform blood samplings and cutaneous tests:** *In order to explore the underlying mechanism (type of reaction)* blood sampling for serology and molecular biology search for viruses involved in DRESS reactions (HHV6, HHV7, EBV, CMV) when possible, tissue biopsy (skin, adenopathy, liver) for typing the kind of lymphocyte infiltration and viral particles reactivation occurring *In order to identify the causal agent* in-vitro lymphocyte transformation tests (coupled with an Elispot assay) on T-lymphocytes cells of the patient, in presence of strontium ranelate or each of the suspected concomitant drugs. epicutaneous patch tests with strontium ranelate or each of the concomitant drugs. *In order to search for pharmacogenomic risk factors* blood sampling for HLA screening (through possible collaboration with the REGISCAR program) **In all populations from our clinical trials database** extensive exploratory analyses for search of risk factors for hypersensitivity reactions	
VTE	- careful monitoring of all VTE in ongoing and planned strontium ranelate studies - specific questionnaires for venous thromboembolic events for patients having such events and additional biological measurements of haemostasis	Information included in section 4.3, 4.4 and 4.8 of the SmPC In order to check the effectiveness of this contra-indication a prescription survey will be carried out. A DHPC circulated to relevant prescribers to inform them of

	parameters for at least patients experiencing such events in on going and planned strontium ranelate studies - VTE from all sources are collected and specifically reviewed in the frame work of PSURs.	this new contraindication
Central nervous system disorders including seizures, disturbances in consciousness and memory loss	- careful monitoring of all CNS events such as Seizures, memory loss and disturbances in consciousness in ongoing and planned strontium ranelate studies - specific questionnaires for patients having such events in ongoing and planned studies - seizures, memory loss and disturbances in consciousness from all sources are collected and specifically reviewed in the frame work of PSURs.	Information included in 4.8 of the SmPC
Creatine Kinase increase and musculosheletal disorders	- careful monitoring of all muscular events and of all Creatine Kinase increase in ongoing and planned strontium ranelate studies - all PSURs focus on this issue and analysis of all cases are collected whatever the source.	Information included in 4.8 of the SmPC
Hepatobiliary disorders: Hepatitis and serum transaminases increased (in association with hypersensitivity)	- Routine Pharmacovigilance activities collecting all reports whatever the source - all PSURs focus on this issue and analysis of all cases are collected whatever the source.	Information included in 4.8 of the SmPC
Psychiatric disorders: confusion, insomnia	- Routine Pharmacovigilance activities collecting all reports whatever the source - all PSURs focus on this issue and analysis of all cases are collected whatever the source.	Information included in 4.8 of the SmPC
Blood cytopenic disorders: bone marrow failure	- Routine Pharmacovigilance activities collecting all reports whatever the source - All PSURs focus on this issue and analysis of all cases are collected whatever the source.	Information included in 4.8 of the SmPC
Potential risks		
Intertitial nephritis (renal and urinary disorders)	Routine Pharmacovigilance activities collecting all reports whatever the source	Not Applicable
Psychiatric disorders: depression and hallucination	Routine Pharmacovigilance activities collecting all reports whatever the source	Not Applicable
Photosensitivity	Routine Pharmacovigilance activities collecting all reports whatever the source	Not Applicable

Pancreatitis	Routine Pharmacovigilance activities collecting all reports whatever the source	Not Applicable
Bone sarcoma	Routine Pharmacovigilance activities collecting all reports whatever the source	Not Applicable
HTA	Routine Pharmacovigilance activities collecting all reports whatever the source	Not Applicable
Potential risk of skeletal accumulation of strontium	Measures taken to provide long term data on bone biopsy (i.e., more than 8 years)were proposed in study CL3-12911-012 [SOTI and TROPOS extension phase]. No biopsy was performed. No more measures are planned at this time in PMO women. In male patients with osteoporosis treated with strontium ranelate, a 3-year non interventional study with the primary endpoint incidence of fractures is proposed for studying the potential risk "bone strontium accumulation in men"	Information included in the section 5.3 of the SmPC
Missing information		
Paediatric group (<18 years)	Routine pharmacovigilance	Information included in the section 4.2 of the SmPC
Pregnancy and breast-feeding	Routine pharmacovigilance	Information included in the section 4.6 of the SmPC
Long term safety in men with osteoporosis	Routine pharmacovigilance Long term safety to be followed in the observational fracture incidence study	Not Applicable
Cardiac events	***Routine pharmacovigilance GPRD study***	***Not Applicable***

The below pharmacovigilance activities in addition to the use of routine pharmacovigilance were proposed by the applicant and supported by the CHMP to investigate further some of the safety concerns:

Description	**Due date**
Observational cohort survey to evaluate the incidence of fractures and the adherence and tolerability of strontium ranelate in osteoporotic men treated with strontium ranelate in the post-marketing setting. The non-interventional survey is planned for 3-years.	Progress reports with PSURs
Specific study in osteoporotic patients to further assess the risk of ischaemic cardiac events, using the GPRD database. This observational retrospective study will use a population-based cohort to assess the risk of ischemic cardiac events, and a nested case-control study to investigate the potential association with strontium ranelate.	November 2012 (with PSUR)

These pharmacovigilance activities are in addition to those already requested.

No additional risk minimisation activities were required beyond those included in the product information.

Due to the safety concerns discussed above, the new indication in men and the lack of long-term safety data in this population, the MAH was requested by the CHMP to continue to submit 6 monthly PSURs instead of yearly PSURs, unless otherwise notified by the CHMP. The RMP has been updated accordingly to reflect this request.

2.7. Changes to the Product Information

The following changes to the SmPC were agreed following the assessment of all data provided:

4.1 Therapeutic indications

PROTELOS is indicated in adults.
Treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fractures (see section 5.1).
Treatment of osteoporosis in men at increased risk of fracture (see section 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy

~~**PROTELOS is only intended for use in postmenopausal women.**~~
There are no data from the use of strontium ranelate in pregnant women.

5.1 Pharmacodynamic properties

….

Treatment of Osteoporosis in men:
The efficacy of PROTELOS was demonstrated in men with osteoporosis in a 2-year, double-blind,placebo-controlled study with a main analysis after one year in 243 patients (Intention to treatpopulation, 161 patients received strontium ranelate) at high risk of fracture (mean age 72,7 years;
mean lumbar BMD T-score value of -2.6; 28% of prevalent vertebral fracture).
All patients received daily supplemental calcium (1000 mg) and vitamin D (800 UI).
Statistically significant increases in BMD were observed as early as 6 months following initiation ofPROTELOS treatment versus placebo.
Over 12 months, a statistically significant increase in mean lumbar spine BMD, main efficacy criteria (E (SE) = 5.32% (0.75); 95%CI = [3.86 ; 6.79]; p<0,001), similar to that observed in the pivotal anti-fracture phase III studies carried-out inpostmenopausal women, was observed.
Statistically significant increases in femoral neck BMD and total hip BMD (p<0,001) were observed after 12 months.

5.2 Pharmacokinetic properties

Strontium ranelate is made up of 2 atoms of stable strontium and 1 molecule of ranelic acid, the organic part permitting the best compromise in terms of molecular weight, pharmacokinetics and acceptability of the medicinal product. The pharmacokinetics of strontium and ranelic acid have been assessed in healthy young men and healthy postmenopausal women, as well as during long-term exposure **in men with osteoporosis and** postmenopausal osteoporotic women including elderly women.

The following changes to the Package Leaflet were agreed following the assessment of all data provided:

1. WHAT PROTELOS IS AND WHAT IT IS USED FOR

PROTELOS is a non-hormonal medicine used to treat osteoporosis:
- In postmenopausal women **to** reduce the risk of fracture at the spine and at the hip;
- **In men at increased risk of fracture.**

2. BEFORE YOU TAKE PROTELOS

……

Pregnancy and breast-feeding:
~~**PROTELOS is meant for use only in postmenopausal women. Therefore, do**~~ Do not take PROTELOS during pregnancy or when you are breastfeeding. If you take it by accident during pregnancy or breastfeeding, stop taking it straight away and talk to your doctor.

In addition, upon request by the CHMP during the procedure, Annex II has been updated to reflect the fact that the MAH should provide 6-monthly PSURs unless otherwise specified by the Committee.

"PSURs
The MAH will continue to submit ~~**1 yearly**~~ **6 monthly** PSURs, unless otherwise specified by the Committee for Medicinal Products for Human Use (CHMP)."

3. Overall conclusion and impact on the benefit/risk balance

Benefits

Beneficial effects

The submitted non-clinical data provide support for the efficacy of strontium ranelate in male osteoporosis. Prevention/restoration of trabecular bone loss and changes in trabecular architecture were demonstrated in a preventive study over 52 weeks and in a curative study over 44 weeks, respectively, in male orchidectomised rats (a relevant animal model of male osteoporosis). The strontium ranelate dose of 625 mg/kg/day used in the curative study is considered relevant as the achieved exposure correlates to roughly 1.3- to 2-fold the exposure in men.

The pharmacokinetic data provided in males and the comparative population PK/PD data from osteoporotic males and females do not suggest any differences in exposure that would necessitate a dose adjustment in the male population compared to postmenopausal females.

The pivotal trial (CL3-032) to support the new indication is a randomized, double-blind bridging study in men with primary osteoporosis (n=261) treated daily with 2g of strontium ranelate or placebo for two years. BMD at the lumbar spine after one year of treatment was the primary outcome; secondary efficacy criteria analysed were femoral neck and total hip BMD, bone markers and quality of life. Efficacy on the primary endpoint was sufficiently demonstrated: The relative change of measured BMD at the lumbar spine (L2-L4) from baseline to last on treatment value was 7.05±6.00% in the strontium ranelate group (n=161) versus 1.72±4.44% in the placebo group (n=82); the difference between

groups was statistically significant [5.32% (SE 0.75); 95%CI (3.86; 6.79), p<0.001]. Similar results were obtained from a sensitivity analysis adjusted for age and prevalent vertebral fractures. Results from the secondary analyses on the change of femoral neck and hip BMD were in line with the primary outcome.

The effect size of the BMD increase at the lumbar spine for men in study CL3-032 is comparable to that observed in the postmenopausal females in the SOTI and TROPOS studies (integrated analysis) after 1 year of treatment: The relative increase [mean (SE)] from baseline to M12 was 6.38% (0.81) and 7.04% (0.35), in strontium ranelate treated men and women, respectively. Similar effect sizes for both genders were also demonstrated for the absolute change in lumbar BMD and at the femoral neck level.

Uncertainty in the knowledge about the beneficial effects

There is a difference in the effect size between the male and female study populations at the total hip level: the relative change in hip BMD from baseline to 12 months was 1.77% (0.67) in men versus 4.34% (0.13) in PMO women.

Study CL3-032 was not powered to show a statistically significant difference between groups on the reduction of osteoporotic fractures. Overall, the number of new fractures observed in the study was low, with 6 patients (3.5%) in the strontium ranelate group and 4 patients (4.6%) in the placebo group reporting a non-vertebral fracture after 2 years. Assessable X-ray data at baseline and post baseline (under treatment) from 184 patients (120 in the strontium ranelate group and 64 in the placebo group) indicate that the incidence of morphometric vertebral fractures over 2 years (centralised X-ray assessment) was lower in the strontium ranelate than in the placebo group (5.1% and 6.9%, respectively).

Justification of inclusion criteria that will generate a fracture risk of a similar magnitude in the male study population as compared with the postmenopausal females included in the phase III studies is essential for acceptance of the minimum requirement for granting the indication for treatment of osteoporosis in men based on bridging studies. To further substantiate comparable fracture risk of the male and female study populations, the MAH applied the FRAX® tool to the CL3-032 study data. For the female study population fracture risk analyses have been published earlier (Kanis, 2011). There is a considerable difference in the fracture risk estimates between the male and female study population: Men in study CL3-032 had 10-year probabilities of major osteoporotic fracture and hip fracture of 10.1% and 5.4% respectively, versus 24.3% and 13.0%, respectively, as calculated for women in the PMO studies.

Additional analyses comparing the treatment effect in a risk matched female and male population indicate comparable BMD increase and are considered supportive, even if comparability is shown only for the surrogate endpoint BMD and not for the fracture risk.

Secondary analyses of bone turnover markers and quality of life point in the right direction, but do not add strong support. A somewhat different pattern of change of the bone formation marker b-ALP in the male CL3-032 and in the female SOTI study was observed and it was discussed, whether this could be viewed as an index of a gender specific mechanism of action. Based on the provided literature and taking all other bone marker data provided into account, this difference seems to reflect biological differences. The treatment effect on the b-ALP levels in the male CL3-032 study is higher in the strontium ranelate group than in the placebo group at every time point, similar to what was observed in the SOTI study.

Comparability of passive bone strontium content in men and women was questioned in order to clarify if the proportion ΔBMD accounted for by passive presence of strontium in bone might differ between men and women, which then could result in an overestimation of BMD in males. Although some doubt

remains for methodological reasons, the additional analysis of data from non-clinical studies in male and female rats does not seem to indicate a gender specific difference in bone strontium content.

Risks

Unfavourable effects

In general, the safety profile for strontium ranelate in the male osteoporosis study CL3-032 did not markedly differ from that in female osteoporosis studies, where safety evaluation is based on much larger numbers and longer observation periods.

Overall, 63 (24.2%) patients experienced at least one treatment emergent adverse event considered as related to the study treatment by the investigator; 23.1% in the strontium ranelate group versus 26.4% in the placebo group. The system organ classes most commonly affected in the strontium ranelate group were gastrointestinal disorders (6.4%) and skin and subcutaneous tissue disorders (6.9%).

Discontinuation of treatment due to adverse events occurred more frequently in patients in the strontium ranelate group than in the placebo group (13.9% vs. 10.3%). Discontinuation of therapy was mainly due to gastrointestinal disorders similarly reported in both groups (3.5% vs. 3.4%). Treatment emergent adverse events that led to treatment discontinuation more frequently in the strontium ranelate group were skin and subcutaneous disorders, headache and deep vein thrombosis.

In the strontium ranelate group two patients (1.2%) experienced a deep vein thrombosis versus none in the placebo group. According to the GPRD database the overall incidence of DVT in the general male population over 65 years of age is 0.96%. Increased risk of VTE was observed in the female PMO studies and an approximately 50% increase in the annual risk for VTE including PE is described in the EPAR for Osseor/Protelos.

Mild CPK elevations (i.e. values < 3 ULN) were observed in study CL3-032. An impact of treatment with strontium ranelate on skeletal muscle cell integrity had been reported in the female population.

Serious adverse events were more common in the strontium ranelate group than in the placebo group even though numbers of specific serious adverse events did not significantly differ between groups.

Uncertainty in the knowledge about the unfavourable effects

The safety in men with primary osteoporosis observed in the phase III study was broadly similar to that described in women with postmenopausal osteoporosis, but long-term safety data are missing and the number of male patients treated with strontium ranelate is small.

A discrepancy in cardiac events between treatment groups in study CL3-032 was observed and a comparison between cardiac adverse events in study CL3-032 and the PMO studies was requested. A higher percentage of patients in the strontium ranelate group as compared to the placebo group had a medical history of ischaemic coronary artery disease (16.2% versus 11.5%, respectively), in particular, myocardial ischaemia (10.4% versus 3.4%, respectively), glucose metabolism disorders (11.0% versus 6.9%) and hypertension (42.8% versus 39.1%). Thus, the rate of relevant co-morbidities was unbalanced between the treatment groups. Furthermore, it is acknowledged that the trial was not designed to assess cardiovascular safety.

Theoretically, there is some concern regarding potential long-term consequences of skeletal accretion of strontium, though no negative findings have emerged in the female population so far.

Balance

Importance of favourable and unfavourable effects

With the ageing of the population, osteoporosis in men is increasingly recognized as an epidemiologically relevant health problem. According to literature, one out of three osteoporosis-related fractures occurs in men. Osteoporotic fractures can have severe consequences for the mostly elderly individuals and are associated with significant morbidity and mortality. A treatment that achieves reduction of fractures in the increasing population of elderly osteoporotic men at increased risk of fractures can be considered of great benefit at the individual level as well as at a population level.

Pharmacologic therapy for osteoporosis is indicated in men with T-scores below -2.5 or below -1 with a prevalent fragility fracture. Available treatments in this indication are the oral bisphosphonates alendronate and risedronate, and more recently intravenous zoledronate as well as teriparatide have been approved for use in osteoporotic men at high risk of fractures.

The important safety issues of serious skin reactions such as DRESS, SJS and TEN and the risk of VTE associated with strontium ranelate were highlighted and re-assessed in the recent article 20 procedure. It was concluded that the incidence of serious skin reactions is low and no possible mechanism of action has been identified so far. The product information was updated to facilitate early diagnosis and mandate immediate discontinuation of treatment. Use of strontium ranelate was contraindicated in patients with a history of VTE and in temporarily or permanently immobilised patients. Overall, while these adverse events can be serious and even life-threatening, they are rare and measures have been put in place that should help to reduce their occurrence and/or improve the management. Discussion on the effectiveness of these risk minimisation measures will be followed in the PSURs.

While there was a discrepancy in cardiac events between treatment groups in study CL3-032, the study was too small and not powered for assessment of CV safety and important risk factors and relevant co-morbidities were unbalanced between the treatment groups. The relative risk of ischaemic heart disease in the strontium ranelate group compared to placebo was not significantly increased in neither of the phase III trials, with an adjusted hazard ratio of 1.24 [0.49;3.17] in the CL3-032 study, 1.13 [0.95;1.34] and 0.83 [0.58;1.18] in the TROPOS and SOTI studies, respectively.

Benefit-risk balance and discussion on the benefit-risk assessment

Showing efficacy in fracture risk reduction is regarded as the most relevant endpoint in trials of osteoporosis treatments. For strontium ranelate, efficacy in fracture risk reduction was shown in studies in PMO women. Changes in BMD correlate to the decrease in fracture risk. BMD measurement is therefore considered a valid surrogate endpoint in bridging studies. If the conditions of the bridging approach are fulfilled, efficacy based on BMD increase can be concluded.

The Osteoporosis guideline (CPMP/EWP/552/95 Rev.2) defines minimal requirements for granting an indication for the treatment of osteoporosis in men at increased risk of fracture. As far as duration of the study and justification of the dose are concerned, the present application fulfils these requirements. Inclusion criteria chosen for men in the pivotal study should "generate a fracture risk of a similar magnitude compared with the postmenopausal women that were recruited in the studies used to obtain the indication *Treatment of postmenopausal osteoporosis in women at increased risk of fracture*". The guideline does not provide exact guidance on how the bridging from a male osteoporosis study to earlier PMO studies with the same drug should be undertaken.

The fracture risk calculated with the FRAX tool clearly differs between the male and female phase III study populations: The 10-year probabilities of major osteoporotic fracture and of hip fracture were 10.1% and 5.4% respectively, for men in study CL3-032, versus 24.3% and 13.0%, respectively, for

women in the PMO studies. The MAH attributes the large risk difference to the weight of prevalent osteoporotic fractures in the FRAX model: 28.0% of the men in study CL3-032 had prevalent vertebral fractures versus 48.1% of the PMO women; 36.0% of the men versus 63.5% of the PMO women had any prevalent osteoporotic fracture at baseline.

It is acknowledged that it would have been difficult to include men with 2 or more prevalent fractures in a two-year placebo-controlled study, given that effective treatment is available. It is also agreed that the male trial population was of sufficiently high fracture risk to justify anti-osteoporosis treatment in accordance with current treatment guidelines. Finally, a recent publication suggests that the effectiveness of strontium ranelate on clinical fractures and morphometric fractures in PMO women is comparable over the whole range of FRAX probabilities (Kanis 2011). Still, from a strictly regulatory point of view, the requirement of the applicable osteoporosis guideline is not fulfilled in this respect.

Additional analyses comparing the treatment effect in a risk matched female and male population indicate comparable BMD increase and are considered supportive, even if comparability is shown only for the surrogate endpoint BMD and not for the fracture risk.

The GL further postulates that the magnitude of the BMD changes versus placebo should be similar to that observed in PMO women. Treatment effects in men were similar to those observed in the female study population at the lumbar spine and femoral neck. There is a difference in the effect size at the total hip level: the mean (SE) relative change in hip BMD from baseline to 12 months was 1.77% (0.67) in men versus 4.34% (0.13) in PMO women. However, divergent effect sizes in men and women of a similar range have been observed for other anti-osteoporotic drugs at the hip level. And a different distribution of trabecular and cortical bone, with more trabecular bone in PMO women than in men of the same age leading to greater BMD increases at the hip level, could be a plausible biological explanation.

Finally, the GL states that the observed BMD changes should be proportional to the decreased incidence of fractures in treated women. This was shown in a post hoc analysis of the SOTI and TROPOS data, where every 1% increase in femoral neck BMD was associated with a 3% reduction in the risk of a new vertebral fracture.

Given the remaining restraint with regard to comparable fracture risk of the male and female study populations, the MAH proposes to conduct an observational cohort survey to evaluate the incidence of fractures and the adherence and tolerability of strontium ranelate in osteoporotic men treated with strontium ranelate in the post-marketing setting. The non-interventional survey is planned for 3-years and would include 3000 men with primary osteoporosis, according to sample size calculations. The MAH assumes that approximately 162 fractures would be observed during the 3-year follow up. At entry in the trial, the necessary information to calculate a 10-year fracture risk using FRAX (Kanis 2008) will be recorded. This proposal is supported and it is considered that such an observational survey could indeed yield meaningful information on the efficacy and safety of strontium ranelate treatment of male osteoporosis in clinical use.

Finally, to address some limitations concerning the evaluation of cardiovascular safety the MAH proposes to perform a specific study in osteoporotic patients to further assess the risk of ischaemic cardiac events, using the GPRD database. This observational retrospective study will use a population-based cohort to assess the risk of ischemic cardiac events, and a nested case-control study to investigate the potential association with strontium ranelate. Multivariate analyses taking into account risk and confounding factors will be implemented. This proposal is endorsed.

Moreover, due to the safety concerns addressed above, the new indication in men and the lack of long-term safety data in this population, the MAH should continue to submit 6 monthly PSURs instead of yearly PSURs, unless otherwise notified by the CHMP.

In summary, BMD in lumbar spine (primary efficacy parameter) as well as secondary efficacy parameters total hip BMD and femoral neck BMD were significantly better after 12 months treatment with strontium ranelate, as compared to placebo. Further, results are comparable with those previously demonstrated in a female postmenopausal osteoporosis population.

Taking into account all the evidence provided in this application and considering also the updated RMP including the proposed post-marketing studies, it is concluded that the benefit-risk balance of strontium ranelate in the applied indication "treatment of osteoporosis in men at increased risk of fractures" is positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include 'treatment of osteoporosis in men at increased risk of fracture'. Consequently, sections 4.1, 4.6, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, upon request by the CHMP, Annex II has been updated to reflect the fact that the MAH should provide 6-monthly PSURs unless otherwise specified by the Committee.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Conditions and requirements of the marketing authorisation

PSUR cycle

The MAH will continue to submit 6-monthly PSURs, unless otherwise specified by the CHMP.