Appendix 1

A response by Servier to the Statement of reasons provided by NICE

Correspondence with EMA

The European Agency for the Evaluation of Medicinal Products
Pre-authorisation Evaluation of Medicines for Human Use

London, 20 November 2003
Doc. Ref: EMEA/CPMP/31689/03

CPMP Day 120 List of Questions

Protelos/Osseor
(Strontium ranelate)

EMEA/H/C/560 & EMEA/H/C/561

Applicant: Les Laboratoires Servier

Rapporteur:	Dr. Per Nilsson
Co-Rapporteur:	Prof. Josef Suko
Start of the procedure:	2003-07-21
Date of this report:	**2003-11-11**

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VI. CPMP LIST OF QUESTIONS

VI.1 Quality aspects

Major objections

Drug substance
None.

Drug product
None.

Other concerns

Drug substance

[redacted]

20. [redacted]

VI.3 Clinical aspects

Major objections

Pharmacokinetics
None

Pharmacodynamics
None

Efficacy

1. Indication treatment of postmenopausal osteoporosis

[redacted]

- ✓ Efficacy at the non-axial fracture site of primary interest for a therapeutic claim, *i.e.* upper femur has not been demonstrated in presented analyses. For completeness, data should be presented also for the subset with established osteoporosis (*i.e.* BMD T-score <-2.5 and prevalent fragility fracture).

2. Indication prevention of postmenopausal osteoporosis

[redacted]

Safety

[redacted]

Document title	**RESPONSES TO CPMP DAY 120 LIST OF QUESTIONS** **CLINICAL ASPECTS – MAJOR OBJECTIONS** **EFFICACY**
	QUESTION 3.1
Short title	**Efficacy in reducing the risk of non-axial fracture including hip fracture**
Test drug	**Strontium ranelate (S12911)**
Indication	**Prevention and treatment of post-menopausal osteoporosis**
Company/sponsor	**Institut de Recherches Internationales Servier** **6 Place des Pléiades** **92415 Courbevoie Cedex – France**
Date	**Final Version: 5 February 2004**

CONFIDENTIAL

QUESTION 3.1

Indication treatment of postmenopausal osteoporosis

[redacted]

- ✓ **Efficacy at the non-axial fracture site of primary interest for a therapeutic claim, i.e. upper femur has not been demonstrated in analyses presented. For completeness, data should be presented also for the subset with established osteoporosis (i.e. BMD T-score <-2.5 and prevalent fragility fracture).**

RESPONSE

Executive summary

[redacted]

- **Efficacy at the non-axial fracture site of primary interest for a therapeutic claim, i.e. upper femur has not been demonstrated in analyses presented. For completeness, data should be presented also for the subset with established osteoporosis (i.e. BMD T-score <-2.5 and prevalent fragility fracture).**

Background

Although the relative risk of experiencing a hip fracture was reduced by 15% in the FAS of TROPOS, this reduction did not reach statistical significance (p=0.33) since the TROPOS study was neither powered nor designed to specifically demonstrate a reduction of the risk of hip fracture with strontium ranelate. The TROPOS trial was set up in 1996, i.e., more than one year before the release of but in line with the first CPMP guideline on osteoporosis in 1997 and the FDA guideline issued in 1994. However, non-axial fractures including hip were documented separately, as requested in the CPMP guideline issued in 2001 (CPMP/EW/552/95 rev 1). Moreover, a placebo-controlled study based on rare events such as hip fractures as primary criterion would have led to expose a much larger population to the test product while the safety and efficacy of the tested product in an aged population was not totally established at the beginning of the phase III program: in the target population (with a 1% incidence per year of hip fracture, as observed in the placebo group in TROPOS, and with a 15-20 % theoretical difference between groups at 3 years) 24600 and 13600 patients per group, respectively, would have needed to be followed and analysed as in a phase III to ensure a 90% power to establish superiority (at the type one error rate of 5%).
In the analysis performed in the PP (minimal exposure of 18 months), the RRR was significant (p=0.025) and reached 41% for hip fractures demonstrating that strontium ranelate is also effective on this specific site in women with an adequate compliance to therapy. Although different selection criteria among treatment groups were set up, the PP could be considered as representative of the FAS and similar between treatment groups and therefore reinforced the interest of this PP analysis.
As reminded earlier, for major osteoporosis-related peripheral fractures including the hip site and corresponding to the more relevant sites for osteoporotic fractures, the relative risk of experiencing an incident fracture was significantly reduced by 19% in the FAS ($p = 0.031$), by 21% in the SUB FAS-6 months ($p = 0.018$) and by 35% in the PP ($p < 0.001$) over 3 years.
These results confirm the strengthening of treatment benefits with minimal exposure to strontium ranelate (18 out of 36 months) and further support the non-axial and hip anti-fracture efficacy of the drug.

Confirmation of efficacy on upper femoral fractures: results of a new analysis of TROPOS in patients (FAS) at very high risk of upper femoral fracture

In elderly and frail patients, non-axial fractures comprising hip fractures cause significant suffering and often require hospitalisation. Hence, the risk reduction of this type of fractures is clinically relevant. In particular, hip fractures are associated with considerable morbidity and have mortality at 6 months of 15-20%. Only approximately one-third of hip fracture sufferers return to their former level of independence and the financial costs of hip fracture are proportionally much larger than those for other fractures.
In order to validate a subset of severe osteoporotic patients in our studied population, the incidence over 3 years of hip fractures was estimated among several classes of the most important prognostic factors in the placebo group of the IAE: femoral BMD, prevalent fragility fracture and age.
A clear increase in the risk of hip fracture was observed for patients from the placebo group of the IAE with a femoral neck BMD T-score < -3 (see Table (3.1) 6).
Concerning T-score BMD, it is of note that the femoral neck BMD T-score was calculated according to the centralized normative data (D.O. Slosman), references used for the phase II and phase III studies (homogeneity of the data). As a matter of fact, a femoral neck BMD T-score equal to –3.0 according to this normative data corresponds to –2.4 according to the NHANES normative range. Therefore a threshold of –3.0 according to the normative data used for phase II and III was retained to define the threshold of BMD corresponding to a high-risk group.

Table (3.1) 6 : IAE. - Percentage of patients with a new incident osteoporosis-related hip fracture over 3 years in the placebo group of the FAS, by femoral neck BMD T-score group

			Placebo
Statistical analysis			
]...;-3.50]	N		746
	E / 95% CI	(1)	6.74% / [4.63%;8.85%]
]-3.50;-3.00]	N		962
	E / 95% CI	(1)	3.14% / [1.86%;4.41%]
]-3.00;-2.50]	N		982
	E / 95% CI	(1)	1.19% / [0.45%;1.92%]
]-2.50;...[	N		556
	E / 95% CI	(1)	1.32% / [0.27%;2.37%]
(1) Estimate of the percentage of patients with a new fracture at 3 years / [95% Confidence Interval of the estimate]			

In our studied population, no clear difference in hip fracture incidence was observed according to the presence or not of fragility fracture (2.7% over the 2053 patients with prevalent fragility fracture and 3.4% over the 1203 patients without) (see table in appendix (3.1) 8).

Concerning the age, a range of 74 years or greater corresponds to the main age inclusion criteria of the TROPOS trial. Furthermore, according to the literature, the incidence of hip fracture rises exponentially with advancing age in women over 74-year old (Donaldson, 1990).

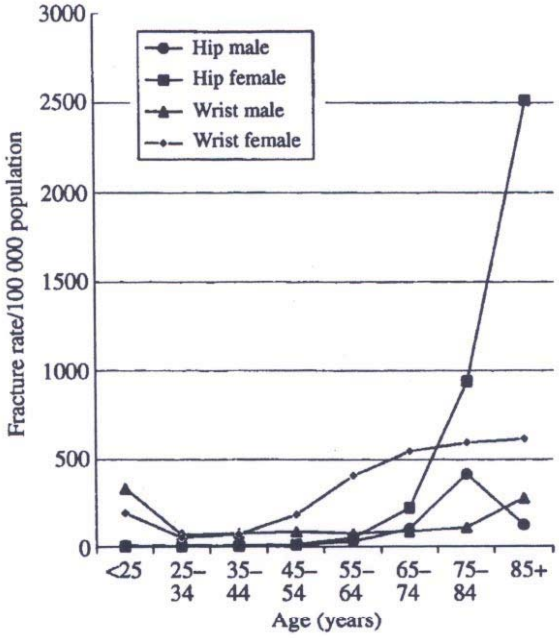


Figure 1. Age- and sex-specific average annual fracture incidence/100 000 population at selected sites. From Donaldson *et al.*[1] (1990)

This increase of hip fractures incidence from 74 years old was confirmed in the IAE where the incidence of the first new hip fracture clearly increased in the placebo group (FAS): 4.42% of patients aged 74 years or above at inclusion presented with a new hip fracture (see Table (3.1) 7) as compared to around 1% below 74 years.

Table (3.1) 7 : IAE. - Percentage of patients with a new incident osteoporosis-related hip fracture in the placebo group of the FAS, by age group at inclusion

			Placebo
Statistical analysis			
]...;70[	N		404
	E / 95%CI	(1)	1.05% / [0.03%;2.07%]
[70;74[	N		898
	E / 95%CI	(1)	1.09% / [0.34%;1.84%]
[74;...[	N		1954
	E / 95%CI	(1)	4.42% / [3.35%;5.49%]
(1) Estimate of the percentage of patients with a new fracture at 3 years / [95% Confidence Interval of the estimate]			

Therefore, to address the CPMP request to complete TROPOS efficacy data at the hip site in patients with established osteoporosis, a FAS subset of patients strongly exposed to the risk of hip fracture was defined, according to the age range (74 years and above) and to the low femoral neck BMD (T-score < -3) at inclusion.

- Baseline characteristics of this subset of patients of 74 years and above with a femoral neck BMD T-score <-3

The baseline characteristics of this subset from TROPOS are summarised in Table (3.1) 8.
A total of 1977 patients (40.1% of the FAS) are represented in this subset: 982 patients in the strontium ranelate group versus 995 patients in the placebo group.
Patients were 74 years and above (mean age: 79.6 ± 4.5 years), with mean menopause duration of 31.5 ± 7.0 years, and a femoral neck T-score ≤ -3 (mean T-score: -3.55 ± 0.48 corresponding to a mean femoral neck BMD of 0.506 ± 0.053 g/cm^2).

Table (3.1) 8: TROPOS -Baseline characteristics of the subset of patients of 74 years and above with a femoral neck BMD T-score ≤-3

	Strontium ranelate	**Placebo**	**All**
	N = 982	**N = 995**	**N = 1977**
Age (years)	**N = 982**	**N = 995**	**N = 1977**
mean (SD)	79.7 (4.6)	79.5 (4.4)	79.6 (4.5)
Menopause duration (years)	**N = 971**	**N = 983**	**N = 1954**
mean (SD)	31.4 (7.0)	31.6 (7.0)	31.5 (7.0)
Min-Max	12-64	15-60	12-64
Femoral neck BMD (g/cm^2)	**N = 982**	**N = 995**	**N = 1977**
Mean (SD)	0.506 (0.053)	0.506 (0.053)	0.506 (0.053)
Mean T-score	-3.55 (0.48)	-3.55 (0.48)	-3.55 (0.48)
Total hip BMD (g/cm^2)	**N = 982**	**N = 995**	**N = 1977**
mean (SD)	0.596 (0.086)	0.593 (0.088)	0.595 (0.087)
Mean T-score	-3.24 (0.85)	-3.28 (0.86)	-3.26 (0.85)
Lumbar BMD (g/cm^2)	**N = 967**	**N = 982**	**N = 1949**
mean (SD)	0.766 (0.153)	0.758 (0.147)	0.762 (0.150)
Mean T-score	-3.16 (1.60)	-3.24 (1.53)	-3.20 (1.57)

Overall, 39.3% of the patients reported at least one prevalent osteoporosis-related non-axial fracture: 39.7% of the patients in the strontium ranelate group and 38.8% in the placebo group (see appendix (3.1) 9).

At inclusion, 34.3% of the patients had at least one prevalent vertebral fracture: 33.0% of the patients in the strontium ranelate group and 35.7% in the placebo group (see appendix (3.1) 9).

- Treatment exposure, treatment intake and global compliance in this subset from TROPOS

The mean treatment exposure until enpoint visit was 807 ± 477 days (mean ± SD), comparable between strontium ranelate and placebo groups.
It is of note that mean treatment exposure was close to mean treatment intake (838 ± 485 days) (see appendix (3.1) 10).
Moreover, 79.5% of the patients, similarly distributed in the two groups, had a satisfactory global compliance (within the [65 – 135]% range) (see appendix (3.1) 11).

- Analysis of study withdrawals in this subset from TROPOS

Overall, 738 of the 1977 patients (37.3% of the patients, 351 in the strontium ranelate group and 387 in the placebo group), well balanced between the two groups, discontinued the study for the reasons listed in Table (3.1) 9.

Table (3.1) 9: TROPOS –Study withdrawals in the subset of patients of 74 years and above with a femoral neck BMD T-score ≤-3

	Srontium ranelate (N=982)	Placebo (N=995)	All (N=1977)
Reason for study withdrawal N(%)	**351 (35.7)**	**387 (38.9)**	**738 (37.3)**
– Adverse event	195	194	389
– Protocol deviation	3	0	3
– Aggravated osteoporosis	1	6	7
– Non medical reason	143	184	327
– Lost to follow up	9	3	12

Study withdrawals in relation with an adverse event were equally distributed in both groups group, whereas study withdrawals due to osteoporosis aggravated or non medical reason were more frequent in the placebo group than in the strontium ranelate group.

- Study withdrawals due to adverse events in this subset from TROPOS

Overall, 389 of the 1977 patients (19.7% of the patients) prematurely discontinued the study due to adverse events (related or not to the study medication): 195 patients in the strontium ranelate group (19.9%) and 194 in the placebo group (19.5%).

Analysis by system organ class and preferred term of adverse events associated to study withdrawal is presented in appendix (3.1) 12.

Three patients in the strontium ranelate group and nine patients in the placebo group were excluded from this analysis because none of the reported adverse events for these patients had "treatment stopped" as action taken.

In both groups, adverse events associated with study withdrawal were mainly gastrointestinal disorders as described for the safety set of TROPOS: 63 patients in the strontium ranelate group and 61 in the placebo group.

Gastrointestinal disorders responsible for treatment withdrawal consisted mainly of nausea, vomiting NOS, abdominal pain upper, dyspepsia, and diarrhoea NOS (see appendix (3.1) 12).

- Emergent adverse events under treatment reported in this subset from TROPOS

In both treatment groups, the most frequently affected system organ classes were the same as those reported in the safety set of TROPOS study:

- Musculoskeletal, connective tissue and bone disorders (44.9% and 43.8% of the patients in the strontium ranelate and placebo groups, respectively).
  The 3 most frequent symptoms (preferred terms) reported in the strontium ranelate group were back pain (11.6% versus 10.3% in the placebo group), localised osteoarthritis (8.1% versus 7.9%) and arthralgia (7.8% versus 7.9%).

- Gastrointestinal disorders (43.2% and 40.7% of the patients in the strontium ranelate and placebo groups, respectively).
  The 3 most frequent symptoms reported in the strontium ranelate group were nausea (7.4% versus 4.7% in the placebo group), diarrhea NOS (7.3% versus 5.8%) and dyspepsia (6.6% versus 5.2%).

- Infections and infestations (38.3% and 39.5% of the patients in the strontium ranelate and placebo groups, respectively).
  The 3 most frequent symptoms reported in the strontium ranelate group were bronchitis (7.3% versus 8.7% in the placebo group), influenza (6.8% versus 7.1%) and urinary tract infection NOS (6.7% versus 6.0%).

- Vascular disorders (26.7% and 24.6% of the patients in the strontium ranelate and placebo groups, respectively).
  The 3 most frequent symptoms reported in the strontium ranelate group were hypertension NOS (12.1% versus 11.8% in the placebo group), hypertension aggravated (1.5% versus 1.0%) and peripheral vascular disease (2.3% versus 2.3%).

- Nervous system disorders (26.2% and 21.4% of the patients in the strontium ranelate and placebo groups, respectively).
  The 3 most frequent symptoms reported in the strontium ranelate group were headache NOS (4.0% versus 2.2% in the placebo group), insomnia NEC (3.6% versus 2.6%) and dizziness (exc vertigo) (3.2% versus 2.2%).

The system organ classes affected by adverse events emergent under treatment are listed in Table (3.1) 10 and appendix (3.1) 13.

Table (3.1) 10: Adverse events emergent under treatment
Analysis by system organ class
in the subset of patients of 74 years and above with a femoral neck BMD T-score ≤-3

Primary system organ class	Strontium ranelate (N=982)		Placebo (N=995)		All (N=1977)	
	NEAE	%	NEAE	%	NEAE	%
Musculoskeletal, connective tissue and bone disorders	441	44.9	436	43.8	877	44.4
Gastrointestinal disorders	424	43.2	405	40.7	829	41.9
Infections and infestations	376	38.3	393	39.5	769	38.9
Vascular disorders	262	26.7	245	24.6	507	25.6
Nervous system disorders	257	26.2	213	21.4	470	23.8
General disorders and administration site conditions	202	20.6	210	21.1	412	20.8
Cardiac disorders	183	18.6	165	16.6	348	17.6
Skin & subcutaneous tissue disorders	166	16.9	171	17.2	337	17.0
Eye disorders	131	13.3	135	13.6	266	13.5
Injury and poisoning	130	13.2	131	13.2	261	13.2
Psychiatric disorders	109	11.1	124	12.5	233	11.8
Metabolism and nutrition disorders	107	10.9	124	12.5	231	11.7
Respiratory, thoracic and mediastinal disorders	122	12.4	107	10.8	229	11.6
Ear and labyrinth disorders	97	9.9	87	8.7	184	9.3
Renal and urinary disorders	76	7.7	59	5.9	135	6.8
Neoplasms benign and malignant (including cysts and polyps)	56	5.7	73	7.3	129	6.5
Blood and lymphatic system disorders	58	5.9	64	6.4	122	6.2
Investigations	41	4.2	48	4.8	89	4.5
Surgical and medical procedures	43	4.4	46	4.6	89	4.5
Hepato-biliary disorders	28	2.9	28	2.8	56	2.8
Endocrine disorders	21	2.1	21	2.1	42	2.1
Reproductive system and breast disorders	15	1.5	22	2.2	37	1.9
Immune system disorders	11	1.1	12	1.2	23	1.2
Congenital and familial/genetic disorders	7	0.7	5	0.5	12	0.6
Social circumstances	1	0.1	1	0.1	2	0.1
ALL	**875**	**89.1**	**888**	**89.2**	**1763**	**89.2**

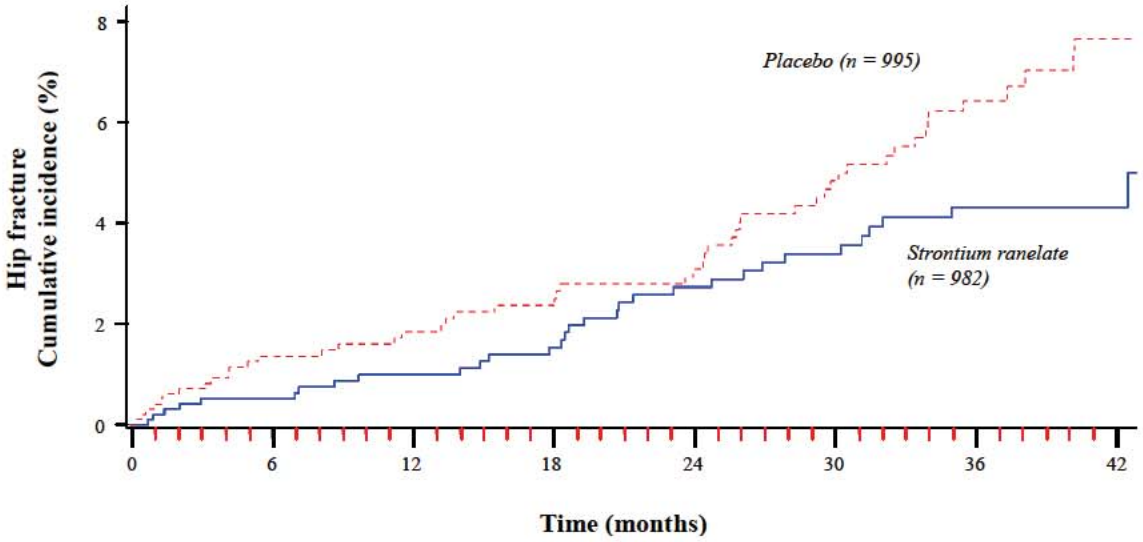
NEAE: Number of patients with at least one Adverse Events Emergent under treatment
N: Number of exposed patients in the considered treatment group
% = NEAE/N x 100

- Efficacy of strontium ranelate in reducing hip and non-axial fractures

Over 3 years, in the FAS analysis (in accordance with the intention-to-treat principle), there was:

- **a 36% RRR of hip fracture (RR = 0.64; 95% CI [0.412; 0.997], p=0.046),**
- and a 23% RRR for all non-axial fracture in the strontium ranelate treated group (RR = 0.77; 95% CI [0.604; 0.984], p=0.036), confirming the efficacy on the main end-point of TROPOS (see Figure (3.1) 2 and tables in appendices (3.1) 14 and (3.1) 15).

Figure (3.1) 2 : TROPOS – Subset of patients of 74 years and above with a femoral neck BMD T-score ≤-3 - Incidence over time of patients with at least one incident osteoporosis-related hip fracture in the FAS (incidence curve)



These data (32 patients versus 51 with an incident hip fracture in the strontium ranelate and placebo groups respectively) assess that strontium ranelate is efficient in reducing the relative risk of hip fracture (RRR=36%, p=0.046) in a subgroup of particular medical interest, i.e., in patients at high risk of hip fracture (patients aged 74 and more with severe osteoporosis according to femoral neck BMD T-score). The incidence at 3 years of patients with at least one new osteoporosis-related hip fracture was lower in the strontium ranelate group than in the placebo group: 4.30% versus 6.40% (see table in appendix (3.1) 14). The estimated number of patients needed to treat (NNT) to prevent one patient from suffering from a new hip fracture is 48 over the 3 years follow-up period.

Rationale for a therapeutic claim on hip fractures

In the elderly, one of the most dramatic consequences of osteoporosis is hip fracture. Therefore, osteoporosis treatments should demonstrate their ability to reduce the incidence of patients with new hip fractures (CPMP/EWP/552/95, 2001). So far, few medications were specifically investigated in trials designed for prevention of hip (or non-axial) fractures in the elderly as primary end-point. As of today, only two molecules (alendronate and risedronate) have been approved in Europe with a specific therapeutic claim for their efficacy at hip level in their SPC. The level of clinical evidence reported in the SPC of these products, which supported such a specific claim, is summarized in Table (3.1) 11 and compared to the strontium ranelate situation.

Table (3.1) 11 : Rationale for a therapeutic claim on hip fractures (comparison to bisphosphonates French SPC)

	Risedronate	Alendronate	Strontium ranelate
RRR for hip fracture	46%	56%	36%
Type of analysis	Post hoc of 2 studies on subgroup defined by medical practice. Pooled data from 2.5 and 5mg groups.	Post hoc of 1 study on subgroup of osteoporotic patients. 5mg for 2 years then 10mg for 2 years.	Post hoc of 1 study on subgroup defined by medical practice. 2g for 3 years.
T-score	< -3 (-2.5 NHANES)	< -2.5 NHANES	≤ -3 (-2.4 NHANES)
Additional risk factors	Prevalent vertebral fracture Age > 70 years	-	Age ≥ 74 years
Subset size/overall population size	NR	37%	40%
Incidence of hip fracture in placebo group	7.4% (over 3 years)	2.2% (over 4 years)	6.4% (over 3 years)
Number of hip fracture (bisphosphonates or strontium ranelate versus placebo groups)	NR 137/6197 versus 95/3134[1]	8 versus 18	32 versus 51
Primary end-point	Hip fracture	Any clinical fractures	Non-axial fractures

NR = Not Reported in the SPC
1 : (McClung M.R., 2001)

Risedronate is the only treatment currently marketed shown to reduce the risk of hip fracture (primary end-point) in pooled data of two identical study protocols involving 9331 elderly women above 70 years. In a sub-group of patients treated for three years (2.5mg or 5 mg), with femoral neck BMD T-score < -3 (-2.5 NHANES) and with previous vertebral fractures, the fracture incidence was reduced by 46% for the hip site. The hip fracture incidence was 3.8% in the pooled risedronate group and 7.4% in the placebo group, respectively.
However, it should be pointed out that this was also a post hoc analysis and that the planned primary analysis failed to demonstrate the efficacy of risedronate on hip fracture in the whole population of the studies. In addition, in patients above 80 years old, risedronate also failed to confirm its beneficial effects at this specific fracture site (RR = 0.8; 95% CI = [0.6;1.2], p = 0.35) (McClung M.R., 2001).

Over 4 years, in post hoc analyses from studies in which hip fracture have been assessed as a secondary end-point, alendronate (5mg/d for 2 years followed by 10 mg/d for 2 years) was shown to reduce the relative risk of hip fracture by 56% but only in women with a femoral neck BMD T-score < -2.5 (NHANES normative range). The number of fractures supporting this result was low: 8 hip fractures in the alendronate group (1.0%) versus 18 (2.2%) in the placebo group, RR = 0.44, 95% CI = [0.18;0.97]. There was no risk reduction amongst women whose femoral neck BMD T-score was greater than -2.5 (Cummings, 1998).

The strontium ranelate results presented here are in line with those of bisphosphonates which have been registered with a therapeutic claim on hip fractures, and this indication was approved on basis of a similar level of clinical evidence as that of strontium ranelate.

- Post-hoc analysis in a subset of severe osteoporotic patients defined by medical practice for their high risk of hip fracture (T-score$\leq$ 2.4 NHANES and age $\geq$ 74 years),
- Level of risk of hip fracture (placebo) similar to that of the risedronate subset in which efficacy was demonstrated,
- Magnitude of effect near 40% with strontium ranelate, similar to that reported for risedronate,
- Robustness of the results: population of about 2000 patients, representing 40% of the FAS, high number of critical events (32 hip fractures in strontium ranelate group versus 51 in placebo group).

In summary, strontium ranelate thus compares favorably with other interventions for osteoporosis, with efficacy at the hip site in patients aged 74 and more with severe osteoporosis according to femoral neck BMD T-score, the population which is the most exposed to hip fractures. The large number of hip and other non-axial fractures make the data robust.

Conclusion

Fracture is the only important outcome of osteoporosis and thus the aim of treatment of osteoporosis is to prevent all fractures. The TROPOS study was specifically designed to address the issue of the efficacy of strontium ranelate on non-axial fractures, as recommended in the 1997 CPMP guideline, and statistically and clinically conclusive results were provided.

- A statistically borderline 15-16% reduction in all **non-axial fractures** at end-point in the FAS was obtained over a 3.0 years mean follow-up, confirmed with additional data provided by a longer follow-up (mean follow-up of 3.8 years): 17-18% statistically significant reduction (p-value ranging from 0.014 to 0.022 depending on the adjustment process).
- A body of additional results reached statistical significance (and even increased the RRR) based on different analyses carried out to improve the sensitivity of the statistical model (adjusted analyses) or to take into consideration patients with treatment exposure duration of at least 6 months or with more adequate compliance (FAS 6 months and PP).

- Moreover, efficacy of strontium ranelate on non-axial fractures was demonstrated in the prospective IAE (p=0.033) and in the PP population (33% non-axial fractures RRR, adjusted p=<0.001).

When focusing on the more relevant sites for osteoporotic fractures (**major osteoporosis fractures**: hip, wrist region, pelvic-sacrum, ribs sternum, clavicle and humerus), in the FAS population, the relative risk was statistically reduced by 19% (unadjusted analysis p=0.031 and adjusted p-value ranging from 0.023 to 0.027 with or without substitution of missing covariates). Furthermore, in women shown to be compliant with therapy (PP population), these results were confirmed (35% RRR for major osteoporosis-related fractures, p<0.001) and for the hip location the reduction was significant (RRR: 41%, p=0.025) showing that strontium ranelate is also clearly effective on this specific location.

The relative risk of experiencing an incident **hip fracture** was also significantly reduced in a subset of the FAS consisting in women of 74 years old and over, with more severe osteoporosis (femoral neck BMD T-score ≤-3, calculated according to the centralized normative data (D.O. Slosman) used for the phase II and phase III studies and corresponding to –2.4 according to the NHANES normative range). In this subset of patients representing 40.1% of the TROPOS study population, there was a statistically significant reduction in hip fracture (36%, p=0.046) in addition to a 23% reduction in all non-axial fracture (p=0.036). These data demonstrate that strontium ranelate is efficient in a subgroup of particular medical interest, strongly exposed to the risk of hip fracture such as patients of 74 years old and over with more severe osteoporosis according to femoral neck BMD T-score. These figures compare favourably with bisphophonates, which have been registered with an indication on hip fracture. This therapeutic claim was granted on the basis of similar proofs of efficacy as strontium ranelate.

In summary, conclusive results are provided on the reduction of the occurrence of first non-axial fracture with strontium ranelate in TROPOS (with statistical significance in adjusted analyses), confirmed by analyses which take into consideration patients with treatment exposure duration of at least 6 months or with more adequate compliance (FAS 6 months and PP) and by additional long-term data. In the pre-planned IAE, statistical significance was reached in both non-adjusted and adjusted analyses. Finally, clear and robust evidence of efficacy of strontium ranelate on the hip fractures was provided in women of 74 years and above with a femoral BMD T-score lower or equal to –3.0.

When taken altogether, these results demonstrate the efficacy of strontium ranelate in the treatment of postmenopausal osteoporosis to reduce the risk of non-axial fractures, including at the site of primary interest for a therapeutic indication, i.e., at the hip level.

The European Agency for the Evaluation of Medicinal Products
Pre-authorisation Evaluation of Medicines for Human Use

London, 22 April 2004
Doc. Ref: EMEA/CPMP/1592/04

Day 180 List of outstanding Issues

Protelos/Osseor
(Strontium ranelate)

EMEA/H/C/560 & EMEA/H/C/561

Applicant: Les Laboratoires Servier

Rapporteur:	Dr. Per Nilsson
Co-Rapporteur:	Prof. Josef Suko
Start of the procedure:	2003-07-21
Date of this report:	**2004-04-15**
CPMP discussion:	April 2004

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IV. LIST OF OUTSTANDING ISSUES TO BE ADDRESSED IN AN ORAL EXPLANATION AND/OR IN WRITING

IV.1 Quality

[redacted]

IV.2 Non-clinical

None

IV.3 Clinical

Efficacy

Indication Treatment of postmenopausal osteoporosis

Any approvable therapeutic indication for treatment of postmenopausal osteoporosis needs to focus on vertebral and/or hip fracture. For the latter, the Applicant proposes a new target population, based on *post hoc* analysis. This might be acceptable, but additional evidence of robustness and relevance is requested. The Applicant should present:

- ✓ data for the whole subset of patients with baseline femoral BMD T-score <-3 (<-2.4 NHANES III)
- ✓ four-year data for the proposed target population of patients ≥74 years and femoral BMD T-score <-3 (<-2.4 NHANES III)
- ✓ data illustrating withdrawal pattern over time in the proposed target population

[redacted]

Document title	**RESPONSE TO CPMP DAY 180 LIST OF OUTSTANDING ISSUES** **CLINICAL ASPECTS** **EFFICACY** **ISSUE VI.3**
Short title	**Efficacy in reducing the risk of non-axial fracture including hip fracture**
Test drug	**Strontium ranelate (S12911)**
Indication	**Treatment of post-menopausal osteoporosis**
Company/sponsor	**Institut de Recherches Internationales Servier** **6 Place des Pléiades** **92415 Courbevoie Cedex – France**
Date	**Final Version: 6th May 2004**

CONFIDENTIAL

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- ✓ **data for the whole subset of patients with baseline femoral BMD T-score ≤-3 (≤-2.4 NHANES III)**
- ✓ **four-year data for the proposed target population of patients ≥74 years and femoral BMD T-score ≤-3 (≤-2.4 NHANES III)**
- ✓ **data illustrating withdrawal pattern over time in the proposed target population**

RESPONSE

Executive summary

The TROPOS trial was set up in 1996, *i.e.*, more than one year before but in line with the CPMP guideline (*CPMP/EW/552/95*) (*CPMP, 1997*) where the non-axial fracture was the recommended efficacy end-point.

The relative risk (RR) of experiencing an incident non-axial fracture (primary endpoint) was significantly reduced in the strontium ranelate treated patients.

Although the TROPOS study was neither powered nor designed to specifically address a reduction of the risk of hip fracture with strontium ranelate, a 36% relative risk reduction (RRR) in hip fracture over 3 years was shown in women of 74 years and above, with a femoral BMD T-score ≤ –3.0 (*patients highly exposed to the hip fracture risk*).

As requested by the CPMP at D150 and D180 additional data are provided:

1/ On the hip fracture incidence over 3 years in the broader population of patients with a femoral BMD T-score ≤ –3.0

- A 30% RRR (RR = 0.70; 95% CI [0.473; 1.041]), in hip fracture with strontium ranelate as compared to placebo was shown in the FAS population. Therefore the clinical benefit of strontium ranelate is consistent in a broader population.
- A 32% RRR (RR = 0.68; 95% CI [0.452; 1.019]), in hip fracture in the FAS 6 months (*pre-defined population restricted to patients with at least 6 months of treatment*).
- A 56% RRR (RR = 0.44; 95% CI [0.250; 0.758]), in hip fracture in the Per Protocol set (*PP, pre-defined population, that is in patients with more adequate compliance to treatment: minimal strontium exposure during the first 18 months*).

These results provided consistent clinical evidence of strontium ranelate efficacy in reducing the hip fracture incidence and supplementary proofs of the pharmacological activity of strontium ranelate.

2/ On the hip fracture incidence over 4 years in patients of 74 years and above, with a femoral BMD T-score ≤ –3.0 (patients exposed to a higher hip fracture risk than the previous subset)

- A 31 % RRR (RR = 0.69; 95% CI [0.467; 1.032]), in hip fracture over 4 years as compared to placebo was obtained in the proposed target population of women of 74 years and above, with a femoral BMD T-score ≤ –3.0 (*FAS population, 36% RRR over 3 years*), indicating the clinical relevance of strontium ranelate in reducing hip fracture incidence while considering a longer follow-up period now available, even including patients with poor minimal treatment exposure.
- A 33 % RRR in hip fracture over 4 years was shown in patients treated for at least 6 months (FAS 6 months, RR = 0.67; 95% CI [0.446; 1.009]),
- A 59% RRR in patients with more adequate compliance (PP, RR = 0.41; 95% CI [0.235; 0.701]).

These results provided additional proofs of the pharmacological activity of strontium ranelate and also confirmed the efficacy of strontium ranelate on hip fracture.

3/ Additional results were also provided in the FAS population of patients of 74 years and above, with both lumbar and femoral BMD T-score ≤ –3.0 (patients exposed to a higher hip fracture risk than the two previous subsets)

- a 45% RRR in hip fracture over 3 years (RR = 0.55; 95% CI [0.301; 0.990]),
- a 46% RRR in hip fracture over 4 years (RR = 0.54; 95% CI [0.311; 0.946]).

The conclusion in terms of efficacy on hip fracture previously established appeared robust and consistent, as shown by the analyses performed on the lower risk populations, during a period of longer follow-up, in additional subgroups and for the initial primary endpoint (non-axial fractures) (*see figure 2 for summary of the results*). This body of additional results confirm that strontium ranelate is efficient to reduce the risk of hip fracture in patients of particular medical interest, strongly exposed to the risk of hip fracture such as patients of 74 years old and over with more severe osteoporosis according to femoral neck BMD T-score. These figures compare favourably with those of bisphophonates, which have been registered with an indication for hip fracture on the basis of similar proof of efficacy as for strontium ranelate.

Comprehensive response

To recall information presented to date, the TROPOS trial was set up in 1996 to study the decrease in the occurrence of non-axial fractures in postmenopausal women suffering from osteoporosis treated with strontium ranelate, i.e., more than one year before the release of but in line with the first CPMP guideline on osteoporosis in 1997 (*CPMP/EW/552/95*) (*CPMP, 1997*) and the FDA guideline issued in 1994 (*both defining vertebral and peripheral fractures as recommended endpoint criteria of efficacy*). However, non-axial fractures including hip were documented separately, as requested in the CPMP guideline issued in 2001(CPMP/EW/552/95 rev 1). The primary endpoint of the study was the occurrence of first new non-axial fracture and the RR of experiencing an incident non-axial fracture was significantly reduced in the strontium ranelate treated patients.

As acknowledged by the Rapporteurs in the D150 assessment report, robustness of efficacy results was shown in the primary end-point analysis of TROPOS with a longer follow-up of patients over 4 years (new data up to a cut-off date on 31/12/2002, which led to a mean follow-up of 3.8 years, 10.3 months additional follow-up compared to the cut-off date of the initial analysis of TROPOS: 10/10/2001):

- a 17% RRR in non axial-fracture with strontium ranelate as compared to placebo was shown over 4 years in the FAS population (RR = 0.83; 95% CI [0.712; 0.975]).

When focusing on the more relevant sites for osteoporotic fractures (major osteoporosis fractures: hip, wrist region, pelvic-sacrum, ribs sternum, clavicle and humerus), the efficacy of strontium ranelate in reducing the major osteoporosis-related sites of fractures (*including hip fracture*) shown in the FAS population over 3 years (19% RRR) was also demonstrated with a longer follow-up now avalaible:

- a 19% RRR in the major osteoporosis-related sites of fractures was provided in the FAS population over 4 years (RR = 0.81; 95% CI [0.677; 0.963]).

Although the relative risk of experiencing a hip fracture was reduced by 15% in the FAS of TROPOS, this reduction did not reach statistical significance since the TROPOS study was neither powered nor designed to specifically demonstrate a reduction of the risk of hip fracture with strontium ranelate. The relative contribution of osteoporosis and falls in the cause-relationships of fractures is quite different from one bone site to another. Hip fractures are most often consequences of high-energy trauma. These characteristics probably explain why, to date, no clinical trial of an anti-osteoporosis drug has been able to demonstrate a preventive effect on hip fractures in a prospective intention-to-treat statistical analysis, and why it is only in the populations with the most severe osteoporosis that anti-hip fracture efficacy has been evidenced.

Consequently and as suggested by the CPMP, further analysis on hip fracture was performed showing a 36% RRR (RR = 0.64; 95% CI [0.412; 0.997]) in hip fracture over 3 years (*Full Analysis Set, analysis in accordance with the intention-to-treat principle – FAS – as suggested by the CPMP, see answer to LOQ D120*) in women of 74 years and above, with a femoral neck BMD T-score ≤ –3.0 (*subset of patients highly exposed to the hip fracture risk*). To complete this result on hip fracture in this population of patients of particular medical interest and as pre-planned in TROPOS study, the efficacy of strontium ranelate has been assessed in 2 additional populations: the FAS 6 months and the PP populations, over 3 years in women ≥ 74 years and with femoral neck BMD T score ≤ -3.0 (table 1 and appendix 1).

Table 1: TROPOS - Relative Risk of incident hip fracture over 3 years in patients of 74 years and above with a femoral neck BMD T-score ≤ -3.0: new analyses for FAS 6 months and PP set

	Patients of 74 years and above with a femoral neck BMD T-score ≤ -3.0	
	Strontium ranelate	**Placebo**
FAS		
Total number of patients	982	995
Total number of patients with at least one incident hip fracture	32	51
Relative Risk (RR), SE and 95% Confidence Interval	**RR = 0.64 (0.15); 95% CI [0.412; 0.997]**	
FAS 6 months		
Total number of patients	799	835
Total number of patients with at least one incident hip fracture	29	49
Relative Risk (RR), SE and 95% Confidence Interval	**RR = 0.61 (0.14); 95% CI [0.385; 0.965]**	
PP set		
Total number of patients	437	659
Total number of patients with at least one incident hip fracture	11	43
Relative Risk (RR), SE and 95% Confidence Interval	**RR = 0.38 (0.13); 95% CI [0.193; 0.727]**	

These results showed that, already observed with other end-points, the increase in exposure to strontium ranelate reinforces the efficacy of hip fractures.

✓ **Data for the whole subset of patients with baseline femoral BMD T-score ≤ -3: new analysis**

As requested by the D 180 report of CPMP, it would be reassuring to confirm the robustness and relevance of the above results in a broader population (femoral neck BMD T-score ≤ –3.0) even though the incidence of hip fracture is reduced in such a population at decreased risk for hip fracture (hip fracture incidence in the placebo group equal to 5.17% (see appendix 2) as compared to 6.40% in the more severe population, i.e. without age limitation.

1/ Hip fracture incidence over 3 years in the broader population of patients with a femoral BMD T-score ≤ –3.0 (≤ -2.4 NHANES III)

The data obtained over 3 years for the whole subset of patients with baseline femoral neck BMD T-score ≤ –3.0 are presented hereafter for the 3 pre-planned populations analysed in the TROPOS study, the FAS, the FAS 6 months, and the PP populations (analyses adjusted on country, age, femoral neck BMD and BMI) (see appendix 2).

1.1/ In the FAS population, 2747 patients with baseline femoral BMD T-score ≤ –3.0 were equally distributed across groups: 1374 in the strontium ranelate group and 1373 in the placebo group. Over 3 years, 43 women in the strontium ranelate treated group and 59 in the placebo group had an incident hip fracture. A 30 % RRR in hip fracture was observed with strontium ranelate as compared to placebo (RR = 0.70; 95% CI [0.473; 1.041]).

1.2/ In the FAS 6 months (N = 2323, 1146 in the strontium ranelate group versus 1177 in the placebo group), that is in patients treated for at least 6 months, a 32% RRR observed in the strontium ranelate treated group (RR = 0.68; 95% CI [0.452; 1.019]).

1.3/ In the PP set, an incident hip fracture was recorded in 17 patients in the strontium ranelate group (in 645 patients) against 50 in the placebo group (in 959 patients) and a 56% RRR was observed with strontium ranelate (RR = 0.44; 95% CI [0.250; 0.758]).

Table 2: TROPOS - Relative Risk of incident hip fracture over 3 years in patients with a femoral neck BMD T-score ≤ -3.0

	Patients with a femoral neck BMD T-score ≤ -3.0	
	Strontium ranelate	**Placebo**
FAS		
Total number of patients	1374	1373
Total number of patients with at least one incident hip fracture	43	59
Relative Risk (RR), SE and 95% Confidence Interval	**RR = 0.70 (0.14); 95% CI [0.473; 1.041]**	
FAS 6 months		
Total number of patients	1146	1177
Total number of patients with at least one incident hip fracture	40	57
Relative Risk (RR), SE and 95% Confidence Interval	**RR = 0.68 (0.14); 95% CI [0.452; 1.019]**	
PP set		
Total number of patients	645	959
Total number of patients with at least one incident hip fracture	17	50
Relative Risk (RR), SE and 95% Confidence Interval	**RR = 0.44 (0.12); 95% CI [0.250; 0.758]**	

2/ Consistency between results over 3 years in patients of 74 years and above with femoral neck BMD T-score ≤ –3.0 and patients with femoral neck BMD T-score ≤ –3.0

Clinical consistency is fairly achieved when interpreting strontium ranelate reduction of hip fracture RR in connexion with population risks: the lower risk of hip fracture in this broader population is associated with a consistent benefit of strontium ranelate treatment:

- 30 % in this lower risk population with a mean age of 77.3 ± 5.3 years (Femoral neck BMD T-score ≤ –3.0) (see appendix 2),
- as compared to 36 % in the population aged of 79.6 ± 4.5 years (Femoral neck BMD T-score ≤ –3.0 and age ≥ 74 years).

In summary, despite the lower risk of hip fracture observed in the placebo group in a larger population consisting of patients with a femoral neck BMD T-score ≤ –3.0 (hip fracture incidence at 3 years equal to 5.17%) without age limit criteria as compared to the risk of hip fracture in patients of 74 years and above with femoral neck BMD T-score ≤ –3.0 (hip fracture incidence at 3 years equal to 6.40%), the clinical efficacy of strontium ranelate in reducing the incidence of hip fracture is consistent over 3 years: respectively a 30% and a 36% RRR.

In the FAS population of patients with a femoral neck BMD T-score ≤ –3.0, the difference between groups is clinically significant: over the period of interest, 43 women in the strontium ranelate treated group and 59 in the control group had a hip fracture (see appendix 2).

Moreover, this clinically significant beneficial effects of strontium ranelate in reducing the incidence of hip fracture as compared to placebo are strengthened by the results:

- in patients with at least 6 months of treatment showing a 32% reduction in the RR (39% RRR in the patients of 74 years and above with a femoral neck BMD T-score ≤ -3.0),

- in patients with more adequate compliance to treatment (PP analysis) with a 56% reduction in the RR (62% RRR in the patients of 74 years and above with a femoral neck BMD T-score ≤ -3.0) (see appendices 1 and 2).

These higher RRR in patients treated for at least 6 months (FAS 6 months) or with more adequate compliance (PP) provide additional proofs of the pharmacological activity of strontium ranelate (see figure 2 for summary of the results).

✓ **Four-year data for the proposed target population of patients ≥74 years and with femoral BMD T-score ≤-3 (≤-2.4 NHANES III): new analysis**

As requested by the D180 CPMP report, the data obtained over 4 years for the proposed target population of patients ≥ 74 years with baseline femoral neck BMD T-score ≤ –3.0 are presented hereafter for the 3 pre-planned populations analysed in the TROPOS study: the FAS, the FAS 6 months and the PP populations (analyses adjusted on country, age, femoral neck BMD and BMI) (see appendix 3).

Hip fracture incidence provided by the additional follow-up over 4 years in patients of 74 years and above with a femoral BMD T-score ≤ -3.0 (≤-2.4 NHANES III)

1/ In the FAS, among the 1979 patients, 42 patients had an incident hip femur (in 982 patients) in the strontium ranelate group against 60 patients (in 997 patients) in the placebo group, corresponding to a 31 % RRR as compared to placebo (RR = 0.69; 95% CI [0.467; 1.032]).

2/ In the FAS 6 months (N = 1635), a 33% RRR was obtained in the strontium ranelate treated group (RR = 0.67;95% CI [0.446; 1.009]): 39 patients with an incident hip fracture in the strontium ranelate group (in 800 patients) compared to 58 patients in the placebo group (in 835 patients).

3/ In the PP set, 17 patients had an incident fracture with strontium ranelate (in 437 patients) against 55 (in 659 patients) in the placebo group. The corresponding RRR was 59% (RR = 0.41; 95% CI [0.235; 0.701]) (see figure 2 for summary of the results).

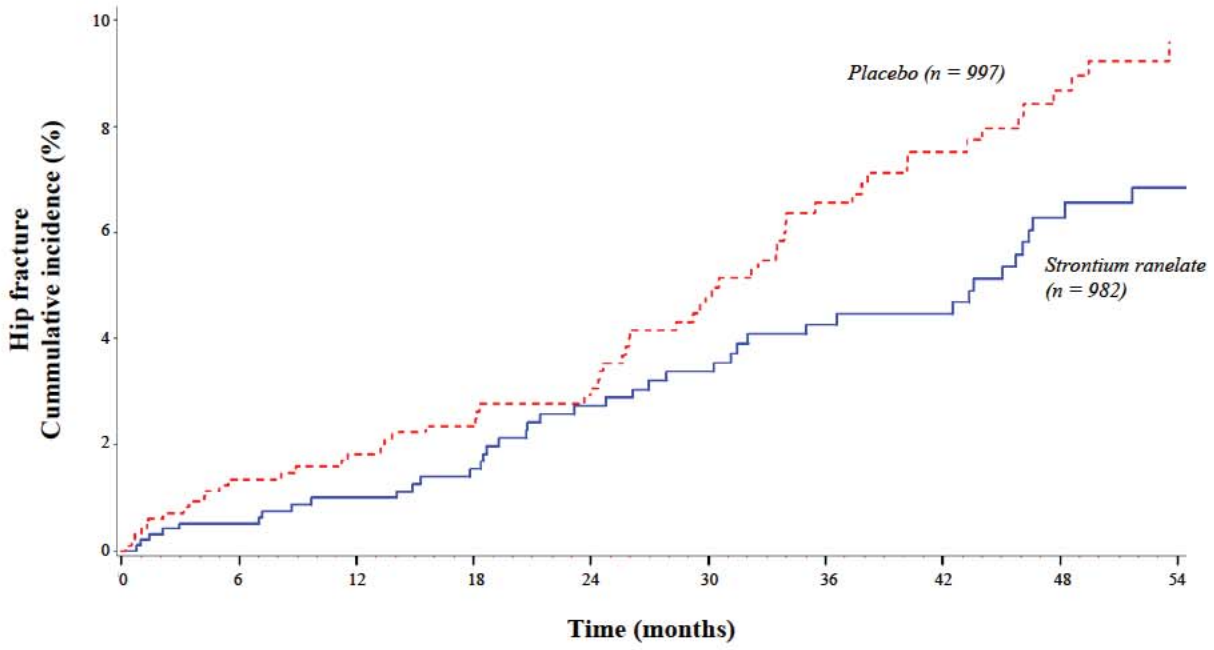
Table 3: TROPOS - Relative Risk of incident hip fracture over 4 years in the subset of patients of 74 years and above with a femoral neck BMD T-score ≤ -3.0

	Over 4 years (cut-off date 31/12/2002)	
	Strontium ranelate	**Placebo**
FAS		
Total number of patients	982	997[(1)]
Total number of patients with at least one incident hip fracture	42	60
Relative Risk (RR), SE and 95% Confidence Interval	**RR = 0.69 (0.14); 95% CI [0.467; 1.032]**	
FAS 6 months		
Total number of patients	800	835
Total number of patients with at least one incident hip fracture	39	58
Relative Risk (RR), SE and 95% Confidence Interval	**RR = 0.67 (0.14); 95% CI [0.446; 1.009]**	
PP set		
Total number of patients	437	659
Total number of patients with at least one incident hip fracture	17	55
Relative Risk (RR), SE and 95% Confidence Interval	**RR = 0.41 (0.11); 95% CI [0.235; 0.701]**	

[(1)] Two more patients were taken into account in the FAS population corresponding to this additional long-term analysis (both of them in the placebo group: 2455 patients for this 4-year cut-off / 2453 patients for initial 3-year cut-off). For these 2 patients, the first post-baseline evaluation concerning the occurrence of non-axial fractures were collected after the initial cut-off by the follow-up procedure on withdrawn patients (one patient reported incident hip fracture after the initial cut-off, the other one had no non-axial fracture).

The figure 1 below illustrates the cumulative incidence of hip fracture for TROPOS study over 4 years (cut-off 31 Dec 2002).

Figure 1: TROPOS – Patients of 74 years and above with a femoral neck BMD T-score ≤ -3.0 - Incidence over time of patients with at least one incident hip fracture in the FAS over 4 years (incidence curve)



- ✓ **In addition to the CPMP D180 request, new analyses of hip fracture incidence are provided in the FAS population of patients of 74 years and above, with both lumbar and femoral BMD T-score ≤ –3.0 (patients exposed to a higher hip fracture risk than the two previous subsets)**

In the FAS analysis of this population of patients exposed to a higher hip fracture risk than the two previous subsets (as both lumbar and femoral BMD T-score are ≤ –3.0 and age ≥ 74), there was:

- a 45% RRR of hip fracture over 3 years, RR = 0.55; 95% CI [0.301; 0.990]) (see appendix 4),
- and a 46% RRR of hip fracture over 4 years, RR = 0.54; 95% CI [0.311; 0.946]) (see appendix 5).

These results give additional evidence of robustness and clinical relevance for the efficacy of strontium ranelate on hip fracture (see figure 2 for summary of the results).

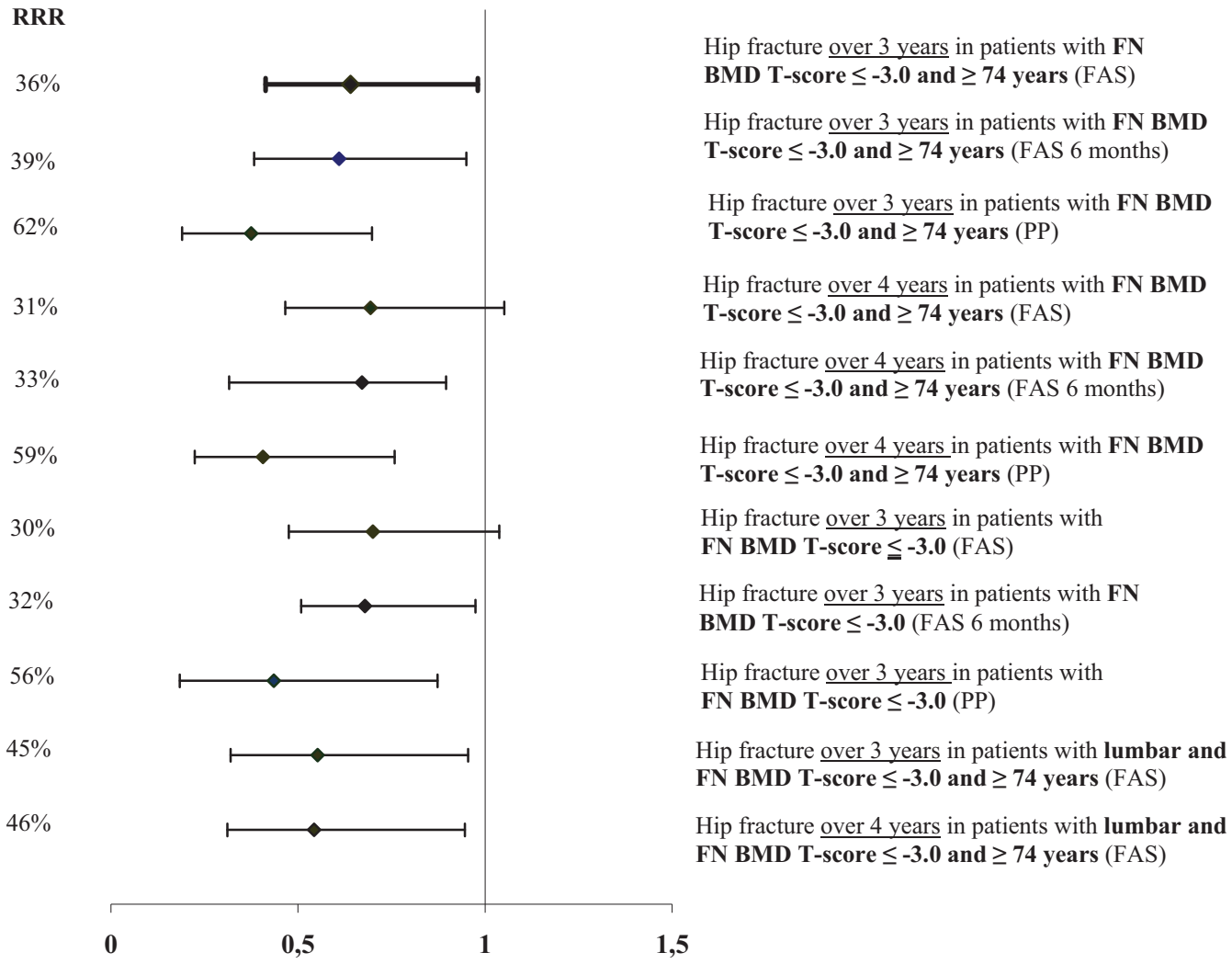
In summary, the results over 3 years provided in patients with a femoral neck BMD T-score ≤ –3.0 illustrated the fact that the RRR was consistent in a broader population slightly less exposed to the risk of hip fracture, and even higher in patients treated for at least 6 months (FAS 6 months) or with more adequate compliance (PP).

Moreover, in the subset of patients of 74 years and above with a femoral neck BMD T-score ≤ -3.0, the conclusive results provided on the reduction of the occurrence of the hip fractures with strontium ranelate over 3 years are clinically confirmed by additional long-term data over 4 years (RRR = 31%) and once more confirmed by analyses which take into consideration patients with treatment exposure duration of at least 6 months or with more adequate compliance (FAS 6 months and PP) with higher RRR (respectively 33% and 59%). These results provided additional proofs of the pharmacological activity of strontium ranelate.

In addition, the RRR of hip fracture obtained in patients exposed to a higher hip fracture risk than the two previous subsets (that is in patients of 74 years and above, with both lumbar and femoral BMD T-score ≤ –3.0) were 45% over 3 years and 46% over 4 years, respectively.
Fractures depend on both the severity of the trauma and the bone fragility. The more severe the level of osteoporosis, the less trauma is required to result in a fracture. Severe osteoporosis is highly implicated in the occurrence of fractures and treatment is therefore beneficial. Conversely, the less severe the level of osteoporosis, the higher the level of trauma required to result in a fracture, and therefore anti-osteoporotic treatment may appear less effective.

Finally, robust evidence of clinical efficacy of strontium ranelate on the hip fractures was demonstrated in women of 74 years and above with a femoral BMD T-score ≤ –3.0.

Figure 2 : Reduction of hip fracture relative risk with strontium ranelate



✓ **Data illustrating withdrawal pattern over time in the proposed target population**

Over 4 years of mean follow-up, 867 of the 1979 patients (43.8% of the patients, 412 in the strontium ranelate group and 455 in the placebo group), well balanced between the two groups, discontinued the study for the reasons listed in table 4.

Table 4: TROPOS –Study withdrawals in the subset of patients of 74 years and above with a femoral neck BMD T-score ≤ -3.0 over 4 years

	Srontium ranelate (N=982)	Placebo (N=997)	All (N=1979) [1]
Reason for study withdrawal N (%)	**412 (42.0)**	**455 (45.6)**	**867 (43.8)**
Adverse event	224	220	444
Protocol deviation	3	1	4
Aggravated osteoporosis	1	7	8
Non medical reason	175	220	395
Lost to follow up	9	7	16

[1] Two more patients were taken into account in the FAS population corresponding to this additional long-term analysis (both of them in the placebo group: 2455 patients for this 4-year cut-off / 2453 patients for initial 3-year cut-off). For these 2 patients, the first post-baseline evaluation concerning the occurrence of non-axial fractures were collected after the initial cut-off by the follow-up procedure on withdrawn patients (one patient reported incident hip fractures after the initial cut-off, the other one had no non-axial fracture).

As previously reported over 3 years, study withdrawals in relation with an adverse event were similarly distributed in both groups, whereas study withdrawals due to osteoporosis aggravated or non medical reason were more frequent in the placebo group than in the strontium ranelate group.

- Analysis of study withdrawals by class of time interval in the subset of patients of 74 years and above with a femoral neck BMD T-score ≤–3.0 over 4 years of follow-up

Evolution over time of reasons for study withdrawals is displayed in table 5.

Table 5: TROPOS –Study withdrawals by class of time interval in the subset of patients of 74 years and above with a femoral neck BMD T-score ≤ -3.0 over 4 years

Class of time interval (months)	Srontium ranelate	Placebo
[0-6[		
Reason for study withdrawal N (%)	147 (15.0%)	139 (13.9%)
Adverse event	96	82
Protocol deviation	0	0
Aggravated osteoporosis	1	1
Non medical reason	48	56
Lost to follow up	2	0
[6-12[		
Reason for study withdrawal N (%)	43 (4.4%)	59 (5.9%)
Adverse event	24	32
Protocol deviation	0	0
Aggravated osteoporosis	0	1
Non medical reason	19	26
Lost to follow up	0	0
[12-18[		
Reason for study withdrawal N (%)	48 (4.9%)	53 (5.3%)
Adverse event	19	24
Protocol deviation	2	0
Aggravated osteoporosis	0	1
Non medical reason	22	26
Lost to follow up	5	2
[18-24[		
Reason for study withdrawal N (%)	29 (3.0%)	40 (4.0%)
Adverse event	16	20
Protocol deviation	1	0
Aggravated osteoporosis	0	1
Non medical reason	11	18
Lost to follow up	1	1
[24-30[		
Reason for study withdrawal N (%)	27 (2.8%)	30 (3.0%)
Adverse event	15	12
Protocol deviation	0	0
Aggravated osteoporosis	0	0
Non medical reason	11	18
Lost to follow up	1	0

Class of time interval (months)	Srontium ranelate	Placebo
[30-36[		
Reason for study withdrawal N (%)	32 (3.3%)	43 (4.3%)
Adverse event	13	21
Protocol deviation	0	0
Aggravated osteoporosis	0	1
Non medical reason	19	20
Lost to follow up	0	1
[36-42[		
Reason for study withdrawal N (%)	33 (3.4%)	34 (3.4%)
Adverse event	19	8
Protocol deviation	0	0
Aggravated osteoporosis	0	2
Non medical reason	14	21
Lost to follow up	0	3
[42-48[		
Reason for study withdrawal N (%)	28 (2.9%)	33 (3.3%)
Adverse event	13	10
Protocol deviation	0	0
Aggravated osteoporosis	0	0
Non medical reason	15	23
Lost to follow up	0	0
≥48		
Reason for study withdrawal N (%)	25 (2.6%)	24 (2.4%)
Adverse event	9	11
Protocol deviation	0	1
Aggravated osteoporosis	0	0
Non medical reason	16	12
Lost to follow up	0	0
Over 4 years		
Reason for study withdrawal N (%)	412 (42.0%)	455 (45.6%)
Adverse event	224	220
Protocol deviation	3	1
Aggravated osteoporosis	1	7
Non medical reason	175	220
Lost to follow up	9	7

As expected in long term clinical trials, the higher percentages of study withdrawal were reported at the beginning of the study.

During the first six months, 15.0% of the patients in the strontium ranelate group and 13.9% in the placebo group discontinued the study. The reasons for study withdrawal were non medical reasons and adverse events (as a matter of interest, in the Phase III Safety Set, the treatment discontinuation due to adverse events was more frequent in the first 3 months of treatment than afterwards in both groups and was slightly more frequent in the strontium ranelate group than in the placebo group).

Conclusion

As the fracture is the only important outcome of osteoporosis, the aim of an anti-osteoporotic treatment is to guard against fractures. The TROPOS trial was specially designed to evaluate the non-axial anti-fracture efficacy of strontium ranelate, as recommended in the 1997 CPMP guideline. Conclusive results were provided on the reduction of the occurrence of first non-axial fracture, confirmed by analyses which take into consideration patients with treatment exposure duration of at least 6 months or with adequate compliance. Clinically relevant and robust evidence of strontium ranelate efficacy on the hip fractures was obtained in patients of 74 years and above with a femoral neck BMD T-score ≤ –3.0.

When studying hip fracture occurrence according to patient risk level, results obtained with strontium ranelate as compared to placebo are robust and clinically relevant.

Thus, the clinical efficacy of strontium ranelate in reducing the hip fracture incidence is consistent in a broader population (patients with femoral neck BMD T-score ≤ –3.0) presenting a lower risk of hip fracture: 30% RRR in comparison with the RRR of 36% obtained in patients with femoral neck BMD T-score ≤ –3.0 and age ≥ 74 years.

Furthermore, the results provided in patients with baseline femoral neck BMD T-score ≤ –3.0 for the 3 populations analysed in the TROPOS study are robust:

- A 30% RRR in hip fracture in this FAS population,
- A 32% RRR in hip fracture in the FAS 6 months restricted to patients with at least 6 months of treatment,
- A 56% RRR in hip fracture in the PP set that is in patients with more adequate compliance to treatment.

In addition, the conclusive results obtained on the reduction of the occurrence of the hip fractures over 3 years with strontium ranelate in women of 74 years and above with a femoral neck-BMD T-score ≤ –3.0 (RRR = 36%) are clinically confirmed by additional long-term data over 4 years: 42 women with a hip fracture in the strontium ranelate group versus 60 in the placebo group, RRR = 31%.
These results are also confirmed by the analyses which take into consideration patients with treatment exposure duration of at least 6 months or with more adequate compliance (FAS 6 months and PP) with higher RRR (respectively 33% and 59%), providing proofs of the pharmacological efficacy of strontium ranelate.

Hip fracture incidence results were also provided in the FAS population of patients of 74 years and above, with both lumbar and femoral BMD T-score ≤ –3.0 (patients exposed to a higher hip fracture risk than the two previous subsets):

- a 45% RRR of hip fracture over 3 years,
- and a 46% RRR of hip fracture over 4 years of follow-up.

All these figures compare favourably with bisphophonates, which have been registered with an indication on hip fracture on the basis of similar proofs of efficacy as strontium ranelate.

In summary, the clinically significant beneficial effects of strontium ranelate in reducing the incidence of hip fracture as compared to placebo are strengthened by this body of additional results obtained in various populations of patients over 3 and 4 years, providing additional proofs

of the pharmacological activity of strontium ranelate and confirming that strontium ranelate is clearly effective on the hip location.

In conclusion, when taken altogether the consistent and conclusive results provided:

- on the reduction of the occurrence of first non-axial fracture with strontium ranelate in TROPOS,
- on the reduction of the occurrence of the major osteoporosis fractures (more relevant sites for osteoporotic fractures), including hip location,
- on the reduction of the occurrence of hip fracture in patients of medical interest,

demonstrate the efficacy of strontium ranelate to reduce hip fractures , *i.e.* the site of primary interest for a therapeutic indication.

Rapporteurs'

Day 180 Joint Response Assessment Report

QUALITY & CLINICAL
Assessment of the response to the CPMP List of Outstanding Issues

Protelos/Osseor
(Strontium ranelate)

EMEA/H/C/560 & EMEA/H/C/561

Applicant: Les Laboratoires Servier

Rapporteur:	Dr Per Nilsson
Co-Rapporteur:	Prof Josef Suko
Start of the procedure:	21/07/2003
Date of this report:	28/05/2004
Deadline for comments:	19/06/2004

ASSESSMENT OF THE RESPONSES TO THE CPMP LIST OF OUTSTANDING ISSUES

[redacted]

Clinical aspects

Clinical Efficacy

Question

Indication Treatment of postmenopausal osteoporosis
Any approvable therapeutic indication for treatment of postmenopausal osteoporosis needs to focus on vertebral and/or hip fracture. For the latter, the Applicant proposes a new target population, based on *post hoc* analysis. This might be acceptable, but additional evidence of robustness and relevance is requested. The Applicant should present:

- ✓ **data for the whole subset of patients with baseline femoral BMD T-score <-3 (<-2.4 NHANES III)**
- ✓ **four-year data for the proposed target population of patients ≥74 years and femoral BMD T-score <-3 (<-2.4 NHANES III)**
- ✓ **data illustrating withdrawal pattern over time in the proposed target population**

Summary of the Applicant's response

The TROPOS trial was set up in 1996, *i.e.*, more than one year before but in line with the CPMP guideline (*CPMP/EW/552/95*) (*CPMP, 1997*) where the non-axial fracture was the recommended efficacy end-point.
The relative risk (RR) of experiencing an incident non-axial fracture (primary endpoint) was significantly reduced in the strontium ranelate treated patients.
Although the TROPOS study was neither powered nor designed to specifically address a reduction of the risk of hip fracture with strontium ranelate, a 36% relative risk reduction (RRR) in hip fracture over 3 years was shown in women of 74 years and above, with a femoral
BMD T-score ≤ –3.0 (*patients highly exposed to the hip fracture risk*).

As requested by the CPMP at D150 and D180 additional data are provided:

1/ On the hip fracture incidence over 3 years in the broader population of patients with a femoral BMD T-score ≤ –3.0

- A 30% RRR (RR = 0.70; 95% CI [0.473; 1.041]), in hip fracture with strontium ranelate as compared to placebo was shown in the FAS population. Therefore the clinical benefit of strontium ranelate is consistent in a broader population.
- A 32% RRR (RR = 0.68; 95% CI [0.452; 1.019]), in hip fracture in the FAS 6 months (*pre-defined population restricted to patients with at least 6 months of treatment*).
- A 56% RRR (RR = 0.44; 95% CI [0.250; 0.758]), in hip fracture in the Per Protocol set (*PP, pre-defined population, that is in patients with more adequate compliance to treatment: minimal strontium exposure during the first 18 months*).

These results provided consistent clinical evidence of strontium ranelate efficacy in reducing the hip fracture incidence and supplementary proofs of the pharmacological activity of strontium ranelate.

2/ On the hip fracture incidence over 4 years in patients of 74 years and above, with a femoral BMD T-score ≤–3.0 (patients exposed to a higher hip fracture risk than the previous subset)

- A 31 % RRR (RR = 0.69; 95% CI [0.467; 1.032]), in hip fracture over 4 years as compared to placebo was obtained in the proposed target population of women of 74 years and above, with a femoral BMD T-score ≤ –3.0 (*FAS population, 36% RRR over 3 years*), indicating the clinical relevance of strontium ranelate in reducing hip fracture incidence while considering a longer follow-up period now available, even including patients with poor minimal treatment exposure.
- A 33 % RRR in hip fracture over 4 years was shown in patients treated for at least 6 months (FAS 6 months, RR = 0.67; 95% CI [0.446; 1.009]),
- A 59% RRR in patients with more adequate compliance (PP, RR = 0.41; 95% CI [0.235; 0.701]).

These results provided additional proofs of the pharmacological activity of strontium ranelate and also confirmed the efficacy of strontium ranelate on hip fracture.

3/ Additional results were also provided in the FAS population of patients of 74 years and above, with both lumbar and femoral BMD T-score ≤–3.0 (patients exposed to a higher hip fracture risk than the two previous subsets)

- a 45% RRR in hip fracture over 3 years (RR = 0.55; 95% CI [0.301; 0.990]),
- a 46% RRR in hip fracture over 4 years (RR = 0.54; 95% CI [0.311; 0.946]).

The conclusion in terms of efficacy on hip fracture previously established appeared robust and consistent, as shown by the analyses performed on the lower risk populations, during a period of longer follow-up, in additional subgroups and for the initial primary endpoint (non-axial fractures) (*see figure 2 for summary of the results*). This body of additional results confirm that strontium ranelate is efficient to reduce the risk of hip fracture in patients of particular medical interest, strongly exposed to the risk of hip fracture such as patients of 74 years old and over with more severe osteoporosis according to femoral neck BMD T-score. These figures compare favourably with those of bisphophonates, which have been registered with an indication for hip fracture on the basis of similar proof of efficacy as for strontium ranelate.

Assessment of the Applicant's response

Hip fracture efficacy in the broader population from TROPOS with FN BMD T-score ≤-3 SD

Three-year placebo group incidence of hip fracture was 5.17%, as compared with 6.40% in patients at risk ≥74 years. Risk reductions with Sr ranelate for FAS, FAS 6 months (patients exposed for at least six months) and PP (patients fulfilling compliance criteria according to blood Sr levels) are given in

the table below. Generally, findings are consistent with the risk reduction identified in the targeted population ≥74 years (RR 0.64; [0.412; 0.997], as discussed in the D150 JAR).

Table: TROPOS - Relative Risk of incident hip fracture over 3 years in patients with a femoral neck BMD T-score ≤ -3.0

	Patients with a femoral neck BMD T-score ≤ -3.0	
	Strontium ranelate	**Placebo**
FAS		
Total number of patients	1374	1373
Total number of patients with at least one incident hip fracture	43	59
Relative Risk (RR), SE and 95% Confidence Interval	**RR = 0.70 (0.14); 95% CI [0.473; 1.041]**	
FAS 6 months		
Total number of patients	1146	1177
Total number of patients with at least one incident hip fracture	40	57
Relative Risk (RR), SE and 95% Confidence Interval	**RR = 0.68 (0.14); 95% CI [0.452; 1.019]**	
PP set		
Total number of patients	645	959
Total number of patients with at least one incident hip fracture	17	50
Relative Risk (RR), SE and 95% Confidence Interval	**RR = 0.44 (0.12); 95% CI [0.250; 0.758]**	

Four-year analysis in proposed target population (patients ≥74 years with FN BMD T-score ≤-3SD)
Compared with the previously presented 3-year data, this included an additional 9 and 8 fractures in the placebo and Sr ranelate groups, respectively. The analysis is summarised in the table below, followed by KM incidence estimates. The point estimate for RRR is consistent with 3-year data and there are no real signs that benefit is lost over time. As in other analyses, the FAS 6 months and PP data support pharmacological effects of Sr ranelate.

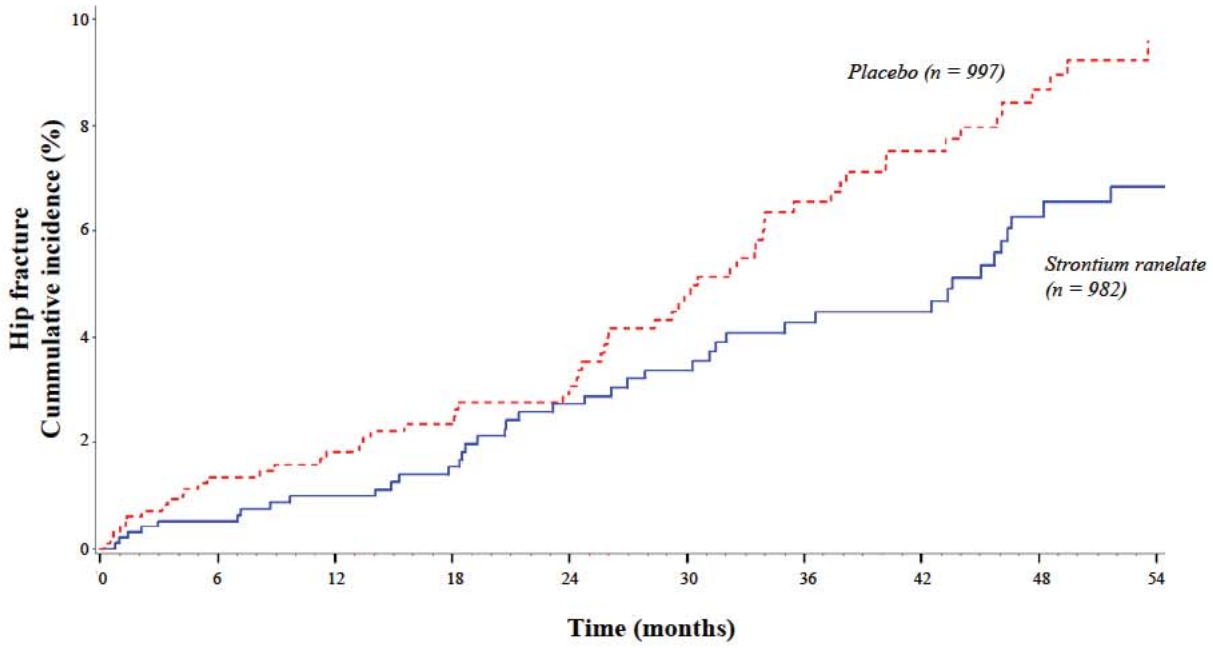
Table: TROPOS - Relative Risk of incident hip fracture over 4 years in the subset of patients of 74 years and above with a femoral neck BMD T-score ≤ -3.0

	Over 4 years (cut-off date 31/12/2002)	
	Strontium ranelate	**Placebo**
FAS		
Total number of patients	982	997[(1)]
Total number of patients with at least one incident hip fracture	42	60
Relative Risk (RR), SE and 95% Confidence Interval	**RR = 0.69 (0.14); 95% CI [0.467; 1.032]**	
FAS 6 months		
Total number of patients	800	835
Total number of patients with at least one incident hip fracture	39	58
Relative Risk (RR), SE and 95% Confidence Interval	**RR = 0.67 (0.14); 95% CI [0.446; 1.009]**	
PP set		
Total number of patients	437	659
Total number of patients with at least one incident hip fracture	17	55
Relative Risk (RR), SE and 95% Confidence Interval	**RR = 0.41 (0.11); 95% CI [0.235; 0.701]**	

(1) Two more patients were taken into account in the FAS population corresponding to this additional long-term analysis (both of them in the placebo group: 2455 patients for this 4-year cut-off / 2453 patients for initial 3-year cut-off). For these 2 patients, the first post-baseline evaluation concerning the occurrence of non-axial fractures

were collected after the initial cut-off by the follow-up procedure on withdrawn patients (one patient reported incident hip fracture after the initial cut-off, the other one had no non-axial fracture).

Figure: TROPOS – Patients of 74 years and above with a femoral neck BMD T-score ≤ -3.0 - Incidence over time of patients with at least one incident hip fracture in the FAS over 4 years (incidence curve)

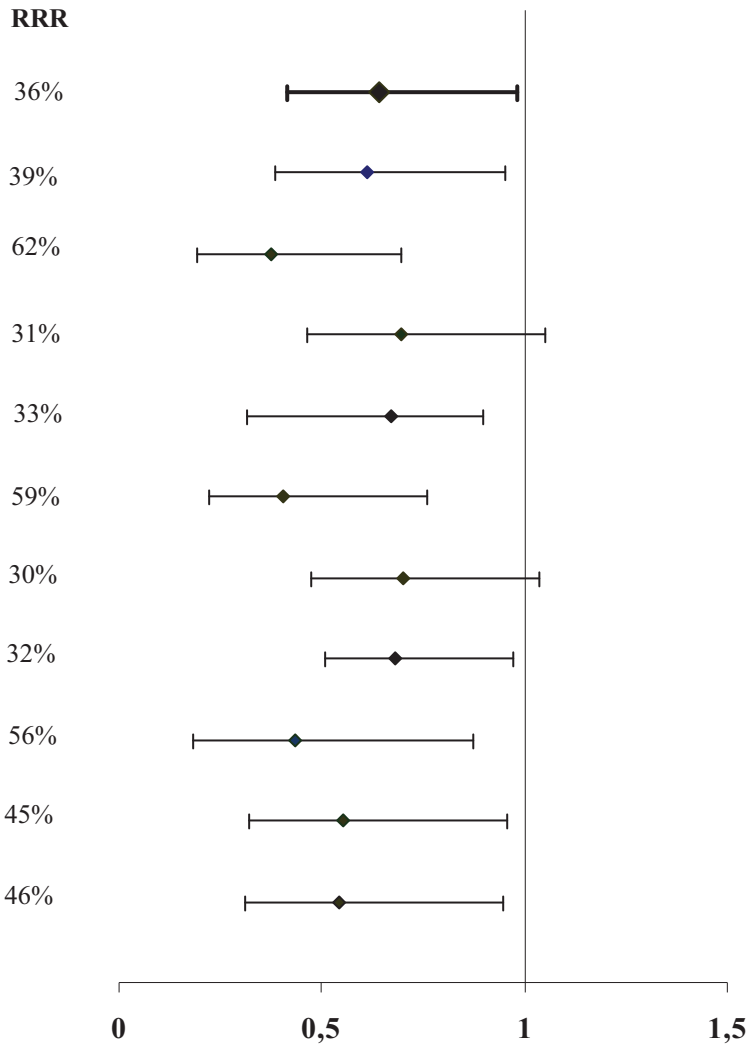


Additional analysis of patients ≥74 years with LS and FN BMD T-score ≤3 SD

For support, the MAH presents data for this subset at particularly high risk (hip fracture incidence over four years in placebo group 9.02%). The analysis was based on a limited number of fractures (19 and 36 in Sr ranelate and placebo groups, respectively) but indicates RR with Sr ranelate over four years = 0.54 (0.31;0.95)

Summary of hip fracture efficacy

A summary of findings in the different population subsets analysed is given below.



Hip fracture over 3 years in patients with **FN BMD T-score ≤ -3.0 and ≥ 74 years** (FAS)

Hip fracture over 3 years in patients with **FN BMD T-score ≤ -3.0 and ≥ 74 years** (FAS 6 months)

Hip fracture over 3 years in patients with **FN BMD T-score ≤ -3.0 and ≥ 74 years** (PP)

Hip fracture over 4 years in patients with **FN BMD T-score ≤ -3.0 and ≥ 74 years** (FAS)

Hip fracture over 4 years in patients with **FN BMD T-score ≤ -3.0 and ≥ 74 years** (FAS 6 months)

Hip fracture over 4 years in patients with **FN BMD T-score ≤ -3.0 and ≥ 74 years** (PP)

Hip fracture over 3 years in patients with **FN BMD T-score ≤ -3.0** (FAS)

Hip fracture over 3 years in patients with **FN BMD T-score ≤ -3.0** (FAS 6 months)

Hip fracture over 3 years in patients with **FN BMD T-score ≤ -3.0** (PP)

Hip fracture over 3 years in patients with **lumbar and FN BMD T-score ≤ -3.0 and ≥ 74 years** (FAS)

Hip fracture over 4 years in patients with **lumbar and FN BMD T-score ≤ -3.0 and ≥ 74 years** (FAS)

Withdrawal pattern over time in the proposed target population
The applicant has provided data to indicate balanced withdrawal over time between treatment arms, as for the entire study population.

Overall Summary and Conclusion
The response is considered acceptable.
The additional analyses presented provide corroborative evidence that, similarly to bisphosphonates, Sr ranelate has (borderline significant) efficacy on hip fracture risk in elderly postmenopausal women with femoral neck osteoporosis. The focus on an identifiable subgroup of medical interest (patients ≥74 years with FN BMD T-score ≤-3 SD (≤-2.4 NHANES III)) was considered acceptable by CPMP and the relevance of the findings in this group gains further support from the four-year data presented with the response.
Issue resolved.

Rapporteurs'

Day 180 Joint Response Assessment Report

OVERVIEW

Protelos/Osseor
(Strontium ranelate)

EMEA/H/C/560 & EMEA/H/C/561

Applicant: Les Laboratoires Servier

Rapporteur:	Dr. Per Nilsson
Co-Rapporteur:	Prof. Josef Suko
Start of the procedure:	2003-07-21
Date of this report:	**2004-05-28**
Deadline for comments:	2004-06-19

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combined calcimimetic activity of extracellular Ca plus Sr evident in treated patients, and direct effects on bone cells, respectively. Mediation of effects on bone cells through the Calcium sensing Receptor (CaR) is proposed as one interesting possibility. This can hardly be the whole explanation since Sr has lower affinity than Ca on the CaR and no type of interaction on CaR has been shown other than agonism, qualitatively identical to that of Ca. Overall, the mechanisms through which Sr may affect bone cells are incompletely elucidated at present.

Any effects of Sr on bone take place in the setting of considerable skeletal accretion of the element, which *per se* is not proposed to contribute to, or detract from the effect on bone mechanical integrity, at levels reached during clinical trial experience so far. Non-clinical and human data are consistent to indicate that accretion occurs mainly through adsorption of Sr to newly formed bone, without effects on hydroxy-apatite crystal structure. Human bone biopsy findings suggest that skeletal accumulation of Sr may reach a plateau after about three years of treatment. The data are sparse, however, and not consistently supported by findings from non-clinical trials. Non-clinical studies demonstrated that high bone concentrations of Sr adversely affect bone mineralisation. This is assumed to be an exaggerated pharmacological effect. The safety margins to clinical exposure are narrow. The Applicant has committed to provide further bone-biopsy data from long-term therapy within ongoing studies.

The dynamics of Sr release from bone off-therapy are not well characterised and it is not known whether all Sr will be eventually released. This concern should, however, be viewed in the light of current acceptance of selective and (for practical purposes) irreversible bone accumulation of bisphosphonates. Further reassurance could be provided post-marketing and is anticipated from off-therapy bone biopsy data within ongoing extension study.

Skeletal accretion of Sr has an unavoidable effect on bone mineral mass assessment through BMD by DXA, which increases markedly during treatment. The relative contributions to ΔBMD of Sr distribution to bone and the higher X-ray absorption of Sr relative to Ca, and "true" increase in bone mineral mass, respectively, must be regarded as somewhat uncertain. Currently, the estimate given in the SPC that 50% of ΔBMD is accounted for by passive presence of Sr in bone appears reasonable based on available data. Remaining Sr in bone likewise affects assessment of BMD off-therapy. Overall, the value of BMD for monitoring of patients on Sr ranelate is uncertain. The prescriber must be alerted that change in BMD in these patients must be interpreted quite differently than during therapy with currently licensed anti-resorptive or anabolic agents. After revision, the SPC is considered acceptable in this respect..

Clinical efficacy

Treatment of postmenopausal osteoporosis

Dose-finding

Doses of Sr ranelate (0.5-2 g/d) tested were selected based on preclinical data and on Phase I tolerability studies, as well as on what highest dose could be considered compatible with long-term compliance. Testing was done in one adequately designed, DB, placebo-controlled, 24M trial in 353 elderly women with established postmenopausal osteoporosis (STRATOS), focusing on change from baseline in lumbar BMD by DXA, expressed as % annual slope. For measured BMD, there was a clear dose-response with all tested doses superior to placebo. BMD adjusted for bone Sr content increased significantly at two years only with the highest dose, Sr ranelate 2g/d. Biochemical markers of bone turnover indicated responses in the direction of decreased resorption and maintained or increased formation, compared with placebo. The decision to bring only the highest tested dose into Phase III is considered acceptable.

Anti-fracture efficacy studies

Summary of clinical efficacy

Efficacy in the treatment of postmenopausal osteoporosis

The efficacy claims were based primarily on M36 analyses on incidences of patients with new fracture from two, large, still ongoing, acceptably conducted, placebo-controlled trials in elderly or very elderly postmenopausal patients with adequately characterised osteoporosis or established osteoporosis.

For reduction of risk of new vertebral fracture, relevant efficacy has been convincingly shown in patients with (SOTI) or without (TROPOS) prevalent vertebral fracture.

As regards efficacy against non-axial fracture, the TROPOS trial was not fully conclusive in its chosen primary endpoint of incidence of patients over three years with (any) new osteoporosis-related peripheral fracture, but a nominally significant effect was indicated in follow-up analysis at four years. A pooled efficacy analysis of SOTI and TROPOS at three years provided borderline significant results that are considered insufficiently convincing for a one pivotal trial /meta-analysis situation. More importantly, CPMP NfG and regulatory consistency would require documentation of benefit for hip fracture prevention for any non-axial treatment claim.

To this end, the Applicant presented *post hoc* subset analyses at three years for a revised target population aged ≥74 years and with femoral neck BMD T-score ≤-3 SD (≤-2.4 SD NHANES III), for which efficacy of the same order of magnitude as shown for bisphosphonates is indicated. This has now been further supported by consistent reisk reduction estimates from four-year follow-up and from the whole TROPOS population meeting the specified BMD criteria. This type of approach has regulatory precedent and is considered acceptable to support a therapeutic indication.

[redacted]