

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Protelos. For information on changes after approval please refer to module 8.

1. Introduction

Osteoporosis is a systemic skeletal disorder characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility. The clinical consequences of osteoporosis are vertebral and peripheral fractures. Postmenopausal osteoporosis affects women after menopause and results from an accelerated rate of bone loss mainly due to oestrogen deficiency. Thus, there is an increase in bone turnover, resulting in a decrease in bone mass and bone mineral density. The bone loss is more accelerated during the first years after menopause, and continues at a slower rate for the lifetime.

There is considerable and recent European regulatory experience with the evaluation of medicinal products for the treatment and/or prevention of postmenopausal osteoporosis, both within the Centralised and MR Procedures. In these evaluations, the requirements outlined in the CPMP Note for Guidance on postmenopausal osteoporosis in women (CPMP/EWP/552/95 rev. 1) have been reasonably consistently applied. Thus:

- Osteoporosis is defined as BMD T score <-2.5 at lumbar spine or hip (meaning proximal femur).
- Osteopenia is defined as BMD T score between -1 and -2.5 .
- Established (severe) osteoporosis is defined as BMD T score <-2.5 in the presence of one or more fragility fractures
- The indication treatment of osteoporosis should be substantiated through placebo- or comparator-controlled studies with the endpoint incidence of patients with new fracture (axial or peripheral). The wording of the indication should reflect the population studied and the efficacy / lack of efficacy documented for the key areas vertebra and hip.
- The indication prevention of osteoporosis requires prior demonstration of anti-fracture benefit in treatment of osteoporosis and may be based on demonstration of efficacy on BMD in postmenopausal women at increased risk of osteoporosis (early postmenopausal with at least one risk factor and late postmenopausal women with osteopenia). If the indication prevention of osteoporosis involves a dose or regimen different from that in treatment of osteoporosis, non-inferiority of the new dose on BMD should be shown in the target population.
- The evaluation of safety, especially bone safety should usually extend over at least three years and incorporate sufficient bone histomorphometric data.

Protelos contains strontium ranelate, a molecule comprised of two atoms of stable strontium (Sr) and one molecule of ranelic acid (RA). Strontium ranelate dissociates at the gastro-intestinal level. Strontium is a cation chemically and physically closely related to calcium (Ca). Ranelic acid is an organic, highly polar molecule without pharmacological activity. Strontium is a bone-seeking element that is suggested to act through dual effects on bone metabolism, by increased bone formation and decreased bone resorption.

The proposed indication is treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.

The recommended daily dose is one 2 g sachet once daily by oral administration. Protelos is intended for long-term use. Protelos should be administered at bedtime, preferably at least two hours after eating, since the absorption of strontium ranelate is reduced by food intake. The product can be taken on an empty stomach.

No dose adjustment is recommended in relation to age, even in the very elderly. No dose adjustment is recommended in patients with mild to moderate renal impairment, while Protelos should not be used in patients with severe renal impairment (in the absence of bone safety data in this population). No dose adjustment is required in patients with hepatic impairment. Efficacy and safety have not been established in children and adolescents and paediatric use is not recommended.

2. Quality aspects

Composition

Protelos contains strontium ranelate as the active substance. The product is presented as granules for oral suspension containing 2 g of strontium ranelate. Other ingredients include aspartame, maltodextrin and mannitol.

Protelos is packaged in sachets composed of a paper/polyethylene/aluminium/polyethylene complex.

Active substance

Strontium ranelate (nonahydrate) is an achiral non-hygroscopic substance, which is produced in a well-characterised single morphological form. The active substance is freely soluble in aqueous media of low pH (< pH 2), but only slightly soluble in neutral aqueous media. Strontium ranelate is practically insoluble in organic solvents.

The active substance is manufactured via a validated process. The critical steps in the synthesis process have been identified and are satisfactorily controlled.

Appropriate specifications have been set for related substances. The origin and mechanism of formation for all possible synthesis impurities and degradation products have been satisfactorily described.

Active substance specification

The active substance specification includes tests for identity, LOD, related substances, heavy metals, pH, strontium content, particle size and assay. The analytical methods used in the routine controls have been suitably described and validated, while the limits for organic impurities have been qualified and accepted based on the levels observed in toxicological studies.

Batch analysis data for all batches used in non-clinical and clinical studies comply with the approved active substance specification.

Stability

The active substance has been subjected to stress testing, photostability testing, and stability studies under long-term, intermediate and accelerated conditions according to ICH guidelines.

Six production scale batches packaged in two types of commercial package were studied under ICH conditions. The parameters evaluated during the stability studies were appearance, water content, IR-spectrum, assay and impurities. The methods employed were validated and stability indicating. The stability data presented support the proposed re-test period for the active substance when stored under the specified conditions.

Other ingredients

All excipients used in the product are of non-animal origin and comply with their corresponding European Pharmacopoeia monographs.

The immediate packaging material consists of a paper/polyethylene/aluminium/polyethylene complex and complies with the Community legislation for materials intended to come in contact with foodstuffs.

Product development and finished product

The objective of the development was to develop an easily dispersible powder without sucrose or sodium, but with a pleasant taste when suspended in water. Mannitol was selected as a filler, maltodextrin as a binder and aspartame as sweetening agent. Among the different formulations tested, the one to be marketed formulation was considered as the best compromise between reconstitution properties, taste, and ease of manufacture.

The manufacture of the finished product is a standard wet granulation process and involves the following steps: mixing, wetting, granulation and drying. The granules produced are subsequently sieved, homogenised and filled into sachets. The manufacturing process has been satisfactorily described and adequately controlled by appropriate in-process controls.

A bioequivalence study has demonstrated the equivalence of the formulation used in the Phase II clinical trials and the one intended for marketing.

Product specification

The specification for the finished product at release and shelf life includes tests for characterisation, average mass, uniformity of mass, pH, microbial quality, identification (organic part and strontium), assay (HPLC), degradation products, assay of strontium and dissolution. All tests included in the specification have been satisfactorily described and validated.

Batch analysis data have been presented from 7 finished product batches. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

Stability of the product

Stability study data have been presented for 3 batches. The samples were packaged in the intended for marketing packaging and stored in compliance with ICH requirements

In addition, one batch was subjected to photo stability studies according to ICH requirements and one batch was subjected to stress testing.

The parameters studied included the ones specified in the shelf life specification. Testing for loss on drying was also performed for information. Data for uniformity of mass, strontium assay and microbial content have also been provided at the start of the stability studies and at selected time points.

The high similarity of the two product strengths and the satisfactory stability results presented support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

Discussion on chemical, pharmaceutical and biological aspects.

The quality of Protelos is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The active substance is stable, well characterised and documented. The excipients are commonly used in these types of formulations and comply with Eur. Phar. Requirements. The packaging material is commonly used and well documented. The manufacturing process of the finished product has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

3. Non-clinical aspects

Introduction

The rat and monkey have been the main species in pharmacology and toxicity studies, the mouse and rat were used for carcinogenicity testing. Available data indicate that these species are adequate models for human safety assessment. The monkey is considered particularly important, being a species with a human-type cortical 'bone remodelling'.

Strontium is distributed predominantly into bone and tooth, and accumulates in these tissues. For a compound with such characteristics, plasma levels may not be the most relevant measure for exposure comparisons. Thus, both plasma and bone exposures are commented on in this assessment. In postmenopausal women treated with 2 g/d, strontium C_{max} of 17±4 mg/l and AUC₂₄ of 341±95 mg.h/l were established, and for ranelate C_{max} of 0.6±0.4 mg/L and AUC₂₄ of 10±7 mg.h/l. Mean iliac crest strontium levels were 1.6% Sr/(Sr+Ca) mmol/mmol after 2-3 years treatment, while an individual bone strontium content up to 3% has been observed after 5 years treatment.

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

The CPMP Note for Guidance (NfG) on postmenopausal osteoporosis in women (CPMP/EWP/552/95 rev1), addresses also non-clinical aspects for a compound to be used in postmenopausal osteoporosis. The applicant has obtained an extensive set of bone quality data (bone from all pivotal pharmacology and toxicity studies has been analysed), in accordance with CPMP/EWP/552/95 rev1, to support primary pharmacodynamics and assess bone safety.

In vitro, strontium increased bone formation, at least in certain pre-osteoblastic cell systems, and inhibited the bone resorption activity of osteoclasts. Strontium induced osteoclast apoptosis at higher concentrations (9 mM). Strontium acted as a full agonist at the Ca sensing receptor (CaR) expressed in non-bone cells, with about 30% lower affinity than Ca. At physiological Ca-levels, EC₅₀s ranged from 0.8-5.7 mM. It is not known if it acts similarly on bone cell CaR, or to what extent the CaR is important for bone cell function. Overall, *in vitro* effects were generally seen at 1 – 20 mM strontium, although apoptosis and CaR Emax occurred at 9-25mM. If these concentrations are relevant for the *in vivo* situation is uncertain. Moreover, the available information is not sufficient to establish by what mechanism strontium mediates its claimed effects on bone turnover.

The pivotal *in vivo* studies are those in OVX animals. The OVX model is characterised by stimulation of trabecular bone turnover and imbalance between bone resorption and formation in favour of bone resorption, leading to bone loss, most pronounced at sites mainly composed of trabecular bone (vertebral body, long bone metaphyses).

Strontium ranelate had modest effects in the **rat** model of ‘treatment of osteoporosis’, *i.e.* when strontium was started at least 8 weeks after OVX. There were positive trends (*e.g.* increased bone mass), but statistical significance was seldom reached. Bone formation appeared maintained, while inhibition of bone resorption was generally non-significant.

In the pivotal rat study to support ‘prevention of osteoporosis’ (up to 625 mg/kg/d for 52 weeks, initiated at OVX), strontium ranelate partially prevented OVX-induced trabecular bone loss. There was no effect on resistance of bone sites consisting predominantly of cortical bone, while significantly increased resistance (high dose only) was seen in lumbar vertebra. The OVX-induced increased bone formation appeared maintained by strontium, while only non-significant trends were seen for inhibition of bone resorption. Week 52 at 625 mg/kg/d, strontium plasma and bone levels were in the clinical range. The Ca content in bone was maintained or increased (0-5%) in the strontium groups.

Two long-term studies were performed in OVX **monkeys**, using a ‘prevention design’. In one study, 125, 250 or 625 mg/kg/d strontium ranelate was given for 30 months. Compared with non-treated OVX monkeys strontium increased bone formation, the MD was most effective. There were also indications of *increased* bone resorption, although less than the increased formation. In the other study, 150 mg/kg/d given during 27 months increased markers of bone formation, and reduced some but not all markers of bone resorption. Strontium ranelate had no significant effects on bone mass or bone strength in either study. In all dose groups, the systemic exposure and bone levels were similar to levels in women given intended therapy.

Data from long-term studies in *intact* rats and monkeys indicated increased bone formation and decreased bone resorption, as well as positive effects on bone dimensions, micro-architecture and bone strength. The data in intact animals are considered of less relevance than those obtained in OVX animals, considering the indication applied. As evident from above, the studies in OVX rats and monkeys provide weak support in terms of efficacy for the intended clinical use in post-menopausal osteoporosis.

- Safety pharmacology

Strontium ranelate did not produce any unexpected or toxic effects in the safety pharmacology studies, which were conducted in accordance with the ICH S7A (CPMP/ICH/539/00). With respect to cardiovascular and specifically QT effects, *in vitro* (HERG channels, rabbit Purkinje fibres) and *in vivo* (dog, monkey single and repeated dosing) data have been obtained. No cause for concern has been identified *in vitro* (concentrations 15 x and 700 x higher than clinical C_{max} for strontium and ranelate), or *in vivo* (C_{max} 7 x and 250 x higher than the clinical C_{max} for strontium and ranelate). In

specific cardiovascular drug-interaction experiments, strontium ranelate did not modify the acute cardiac effects of various drugs acting through Ca-dependent mechanisms, at plasma strontium levels similar to the clinical C_{max}. In murine renal tubule cells, 2 mM strontium or calcium ranelate inhibited (-30%) the 25(OH)D₃-1 alpha-hydroxylase activity, but no effects occurred at 1mM. Specific experiments focussing on ranelate showed that it had no primary pharmacodynamic effects *in vitro*, or any relevant interactions with a large number of receptor systems.

- Pharmacodynamic drug interactions

No drug interaction study was performed.

- Summary of salient findings

In vitro, strontium increased bone formation in certain pre-osteoblastic cell systems, and inhibited the bone resorption activity of osteoclasts. Strontium acted as a full agonist at the CaR expressed in non-bone cells, with lower affinity than Ca. *In vitro*, effects generally occurred at 1 – 20 mM strontium. *In vivo*, long-term dosing of OVX rats and monkeys with strontium ranelate resulted in increased bone formation, but only non-significant trends of reduced bone resorption. In rats, certain positive effects (e.g. on bone mass) were seen but increased resistance was only observed at the highest dose tested for 52 weeks. In OVX monkeys, there were no meaningful effects on bone mass, or bone strength.

Pharmacokinetics

Specific analytical methods were developed to measure strontium and ranelic acid in biological samples. The techniques employed involved elemental spectrophotometry and HPLC analysis, respectively, to determine levels of strontium (as well as calcium) and ranelic acid in samples collected during non-clinical and clinical studies. The methods were validated and their performance, in terms of precision and accuracy, was adequate. In the absence of metabolism of strontium or ranelate, no metabolite was analysed. For distribution and excretion studies, radiolabeled [⁸⁵Sr]-strontium ranelate and strontium-[¹⁴C]-ranelate were used. Some of the centres performing strontium analytic determinations in the rat were not GLP-compliant. Therefore, the applicant performed a bridging study to validate data from these sites, with dose levels covering those observed in the previous non-clinical studies. No apparent difference in exposure was seen in comparison with those seen previously, and the results are thus acceptable.

The pharmacokinetic parameters in the rat and the monkey were calculated using a population kinetic approach, based on available pharmacokinetic and toxicokinetic data. A four- (rat) or three- (monkey) compartment model was fitted to the data. Slight differences for some parameters obtained in the respective models were found when compared with those established in single studies.

Strontium

- Absorption- Bioavailability

The bioavailability of strontium decreases with increasing dose. In rats, F was 20-7% from 75-to 1150 mg/kg strontium ranelate. In monkeys, F_{rel} was 80 - 6% from 9 to 940 mg/kg strontium ranelate. The protein binding of strontium is moderate (25-30%) in rodents, monkey and human.

- Distribution

Tissue distribution has been studied after single and 8 weeks repeated administration in female albino rats. These data show that strontium is distributed predominantly into calcified tissues and accumulates there, while exposure of non-calcified tissues was low. Calcified tissue strontium levels were at least 400 x higher than corresponding blood levels.

Limited data on bone levels over time are available. In rats dosed for 26 weeks and followed thereafter for 26 weeks, C_{max} in bone (~100 x background) was reached one week after the last dose. After 26 weeks recovery, bone and plasma levels were still significantly above background (73x in bone, 16x in plasma). Moreover, bone strontium content determined after 26, 41 and 104 weeks dosing in rats showed accumulation with time (e.g. in femur 3.4%, 3.7% and 4.9% (males) and 2.6%, 2.7% and 4.3% (females) at weeks 26, 41 and 104). Strontium levels in bone biopsies (iliac crest) from OVX monkeys were comparable at 9 and 27, or 12 and 30 months. Although these data are scarce, they do not indicate bone accumulation between 9-27 /12-30 months of treatment. The highest dose was 625 mg/kg/d for 30 months, with an iliac crest level of 2.9 – 3.4 % Sr/ (Sr+Ca). Thus, the available non-

clinical data related to accumulation over time are not consistent, which may be related to species differences in bone turnover. Overall, the non-clinical data are insufficient to assess whether the bone strontium level reaches a plateau.

- Metabolism (*in vitro/in vivo*)

Strontium, being a mineral cation, is not metabolised. After oral administration of ^{85}Sr to rodents, most radioactivities were recovered in feces (80-90%), while 5% or less was recovered in urine. No mass balance data are available for other species. Strontium passes readily into rat milk, and is accumulated there when compared to plasma (73-fold, 24 h after dose). Moreover, strontium was detected in plasma and bone from pups that had been suckling treated dams

- Elimination

Different elimination profiles for **strontium** were seen in rat and monkey, possibly due to longer sampling after treatment in rats. The terminal half-life was 78 days (rats) and 23 days (monkey). In both species, this phase was ~10 % of the total elimination, possibly reflecting slow release from bone. The 'equilibrium' half-life was ~ 8-9 days (rats) and ~ 2-3 days (monkey), predicting that steady state is reached by 6 weeks in rats and 2 weeks in monkey. V_d at steady state was 71 (rat) and 15 l (monkey). The plasma kinetics of strontium appeared time independent, with accumulation ratios upon repeated dosing of <2 in rats and monkey. The elimination profiles in monkey and human were similar (based on comparable data sets).

Ranelate

The oral bioavailability of **ranelate** is low and variable (1-10% rat, 9-17% monkey). Protein binding for ranelate was low (5-30%, in mouse, rat, monkey, human). After single oral administration to hooded rats, distribution of labelled ranelate into tissues other than the GI tract was low, but radioactivity was detected in e.g. bone marrow. By 120 h, no radioactivity remained. Plasma data showed large individual variation, resulting in uncertain pharmacokinetic profiles. After oral dosing, $t_{1/2}$ was 7 h (rat), and 34 h (monkey). In rats, the pharmacokinetics of ranelate appeared time independent. In monkeys, some accumulation was reported (ratio 1.3-3). Ranelate was not metabolised *in vitro*, using hepatic microsomes from rat, rabbit, dog, monkey, and *in vivo* data in the monkey confirmed this observation. The lack of data for mouse is considered acceptable, given the lack of metabolism in all species studied. After oral administration, excretion was slow in rat and female monkey (26% by 24h), and was mainly via feces in all species studied. Excretion into milk was minor. There were no gender effects on the pharmacokinetics of ranelate.

No drug interaction study was performed in animals, which is acceptable. There are no distribution studies in pregnant animals, or either component, which is acceptable, considering the indication applied for

- Summary of salient findings

It has been demonstrated that strontium is predominately distributed into calcified tissues, with at least 400 x higher levels compared with blood. No accumulation was identified in non-calcified tissues, while there is insufficient data in animals to conclude whether bone strontium levels reach a plateau during long-term treatment or not.

Toxicology

- Single dose toxicity

Single dose toxicity studies in rodent, dog and monkey given oral (up to 2,500 mg/kg) or i.v (up to 152 mg/kg) doses revealed no treatment-related toxicity except for some emesis in monkeys. Thus, strontium ranelate has a low acute toxicity.

- Repeat dose toxicity (with toxicokinetics)

Information on long-term effects was obtained in repeat dose toxicity studies with gavage dosing in rats (up to 750 mg/kg/d for 26 weeks) and monkeys (up to 1,250 mg/kg/d for 52 weeks). Data from diet studies related to carcinogenicity in mice (up to 7,500 mg/kg/d for 52 weeks, or 1,800 mg/kg/d for 104 weeks) and rats (up to 900 mg/kg/d for 104 weeks), as well as from pharmacodynamic studies in OVX rats and monkeys provided further information.

Bone and tooth toxicity:

In **OVX rats**, no bone toxicity was generally seen (up to 625 mg/kg/d for 52 weeks). In intact rats, osteomalacia of bones and teeth, subsequent fractures/broken incisors, abnormal bone mineralisation and osteoid tissue accumulation were observed after 41 weeks diet dosing with 1,250 mg/kg/d (M), and 2,500 mg/kg/d (F). The bone mineralisation was normalised after 16-28 weeks recovery. Only females underwent specific bone safety evaluation. No abnormal bone effects were found at < 2x (plasma AUC) and ~ 3 x (bone) the clinical exposure. A specific study of tooth effects was performed in rats. No effects were seen after diet dosing with 625 mg/kg/d for 26 weeks, with a tooth content of 3.1 % Sr/(Sr+Ca). Tooth abnormalities and absence of pigmentation occurred at 1,250 and 2,500 mg/kg/d, at tooth levels of 5.4% (MD) and 9-11 % (HD).

In **mice**, osteomalacia of bones and teeth (including broken incisors), and osteoid tissue accumulation occurred from 5,000 mg/kg/d (52 weeks diet) with corresponding bone strontium content of 7-9%. No mineralisation defect or bone toxicity was seen at 2,500 mg/kg/d (bone levels 4-5%). In the 104 weeks study, incisors discoloration, bone thickening (1,800 mg/kg/d), and long bone deformation (females from 600 mg/kg/d, bone strontium content 4.8%) were observed. Histomorphometric examinations of caudal vertebra revealed no mineralisation defects.

No bone toxicity or mineralisation defects were seen in **OVX monkeys** or in **intact monkeys** treated with 750 mg/kg/d for 26 weeks, or 2x250 mg/kg/d for 52 weeks. However, 2x 625 mg/kg/d for 52 weeks in intact monkeys resulted in delayed bone mineralisation in both sexes. There was no impairment of mechanical properties in any of these studies. At the NOEL, the plasma exposure was in the clinical range. Levels in bone were dependent on type of bone measured. Iliac crest levels, for which human data are available, were about 2x higher in OVX monkeys without signs of bone defects. In intact monkeys, delayed mineralisation was seen at bone levels ~2-3 x (humerus) or 2-3 x (lumbar vertebrae) higher than the clinical iliac crest levels.

Mineral crystallography analyses of bone from the 52 weeks monkey study showed that strontium uptake in bone was roughly dose-dependant but heterogeneous, with ~ twice as high levels in cancellous than trabecular bone, and in new bone vs. old bone. There were no changes in the sub-stoichiometry of apatite, the crystal size and structure, the crystal lattice parameters, the degree of bone mineralisation of the mineral substance or the dissolution rate of bone apatite. After a 10-week recovery 42- 69% of the bone strontium was eliminated.

Clinical signs

Tiptoeing', possibly an indicator of poor general health, was noted in rats from 1,250 mg/kg/d in the diet, after 27 weeks. No other indications of possibly CNS related effects have been found in the non-clinical documentation, including data from standard CNS safety pharmacology studies. Whitish discoloration of faeces due to unabsorbed strontium ranelate (from 275 mg/kg/d in rats and 750 mg/kg/d in monkeys), as well as some soft/liquid faeces, episodes of emesis in monkeys were noted.

Blood / urine

Dose-related increases of *blood alkaline phosphatase* (1.9-fold in rats at 750 mg/kg/d, 1.5-fold in monkeys at 1,250 mg/kg/d) were observed, secondary to the effects of strontium on bone. Changes in *inorganic phosphorus* were seen in rats only (25% increase in blood, 75% decrease in urine at 750 mg/kg/d). Decreased blood *calcium* (up to 10%), and a slight increase of urinary calcium were observed, while the total cation blood concentration (Sr + Ca) was increased (up to 13% in rats, at 2-4 x the clinical exposure). These findings were partially or fully reversible after treatment withdrawal. In addition, marginal effects only were seen on vitamin D, PTH or calcitonin in the long-term studies.

Taken together, strontium ranelate did not cause a detectable imbalance of Ca or phosphorous homeostasis or of hormones regulating these systems in animals.

Urinary stones and bladder changes

In mice, urinary stones (consisting of strontium, oxalate and phosphate), and subsequent inflammatory reactions, bladder wall oedema and /or and hyperplasia of the bladder mucosa occurred from 2,500 mg/kg/d (52 weeks) or 1,800 mg/kg/d (104 weeks), more commonly in males. Similar effects were generally not seen in rats or monkeys (except for 1 rat in one carcinogenicity study). The explanation by the applicant, that mice have higher levels of phosphates and oxalates in urine than other species,

leading to the formation of urinary stones is considered plausible, and thus suggests low relevance for human safety.

Cornea changes

In the pivotal rat carcinogenicity study only, a higher incidence of corneal proliferative vascular changes in the superficial layers of the corneal stroma was seen for mid dose and high dose. The batch of compound used in this study only had an alkaline pH, while the compound used in the other diet studies had a neutral pH. It appears plausible that these lesions were an external injury due to exposure of dust from the diet containing strontium ranelate with an alkaline pH and therefore having a higher irritant potential than the normal diet. Similar effects were not seen in the other diet studies, or any other toxicity study. This finding is not considered of clinical relevance.

- Genotoxicity *in vitro* and *in vivo* (with toxicokinetics)

Strontium ranelate displayed no genotoxic potential under the study conditions.

- Carcinogenicity (with toxicokinetics)

Studies of 104 weeks duration with dietary dosing were performed in B6C3F1 mice (250, 600, 1,800 mg/kg/d), and Fischer 344 rats (males: 150, 300, 625 mg/kg/d, females 225, 450, 900 mg/kg/d). The dose selection is acceptable, as some toxicity was evident and based on experience from previous studies. In both rats and mice, the systemic exposure to strontium of the HD groups were < 2x higher than the clinical exposure. For ranelate, somewhat larger margins were obtained (AUC in mice 5-6x higher, C_{mean} in rats 3-5 x higher than human C_{max}).

Control plasma samples were not analysed in the two carcinogenicity studies. In the pivotal rat study, bone from controls, contained expected strontium background levels. In the 'non-pivotal' rat study, analyses at repeated time points revealed no signs of increased strontium levels in control samples.

In the mouse carcinogenicity study, mortality was low in all groups (6 to 14% males, 18 to 28% females). The overall incidence of benign and malignant tumours was the same in control and treated groups. Statistical analyses indicated significant increases in four tumour types; lymphocytic lymphomas in mid dose females only, hepatocellular adenomas in males only, ovarian adenomas and combined lung bronchiolo-alveolar adenoma and carcinoma in males. It is not considered that any of these are treatment related.

In the rat carcinogenicity study, statistical analyses of neoplastic lesions showed a difference in the incidence of thyroid C-cell carcinomas in males (see Table 2.6.6.2). There was no increase in the incidences of C-cell hyperplasia and/or adenoma and no difference in the combined incidence of C-cell changes between treated males and controls, or in females. Other non-neoplastic and neoplastic findings were consistent with the expected spectrum of background lesions in ageing Fischer 344 rats.

Table: Rats with thyroid C-cell proliferative changes in the main carcinogenicity study. The STP/ARP/AFIP and IARC criteria were used for characterisation of the C-cell tumours

Dose group	Male					Female				
	C0	D0	D1	D2	D3	C0	D0	D1	D2	D3
Dose level (mg/kg)	0	0	150	300	625	0	0	225	450	900
C-cell hyperplasia	17	17	17	8	22	29	13	23	29	21
C-cell adenoma	17	27	8	18	18	13	14	11	13	19
C-cell carcinoma	0	1	4 ^{**}	3	6 ^{##*}	3	3	2	3	2
C-cell adenoma and carcinoma	17	27	12	21	22	16	16	13	16	21
Total C-cell changes (hyperplasia and neoplasia)	27	35	26	28	35	37	24	31	39	33

^{*}, ^{**} Fisher test and Peto test: statistically significant versus C0+D0 for $p < 0.05$ (^{*}) or $p < 0.01$ (^{**})

The finding of C-cell tumours in male rats raised concern; one reason being that it affected an organ of major importance for regulation of bone homeostasis. Calcitonin is secreted by thyroid C-cells if Ca

blood levels increase and enhances Ca uptake in bone. PTH, another important part of this regulation, is secreted by the parathyroid in response to decreased blood Ca, and enhances release of Ca from bone. One possible mechanism for the development of C-cell tumours would imply long-term hypercalcemia, leading to continuously enhanced calcitonin secretion, C-cell hypertrophy, and consequently to C-cell adenoma and carcinoma.

In the long-term rat studies, there was a slight decrease in Ca levels (up to 10%), while total cations Ca+Sr was increased (up to 13%). However, there were no consistent changes of calcitonin, and generally it appears that strontium ranelate did not cause a detectable imbalance of Ca or phosphorous homeostasis or of hormones regulating these systems in animals. Mechanistic data in Fischer 344 rats, indicated that a single challenge with Sr stimulated calcitonin release. However, Sr was 3x less potent than Ca, and the minimum Sr concentration able to induce a significantly increased calcitonin secretion was 3x or 7 x higher than the mean Sr plasma level in the carcinogenicity study, or at clinical use, respectively. Moreover, male F344 rats treated 52 weeks with doses as in the carcinogenicity studies had no increase in thyroid C-cell proliferative lesions or in circulating calcitonin, either at basal conditions or in response to Ca stimulation. In this study, it was shown that the Ca levels remained unchanged with age, but the calcitonin levels increased 8-fold in controls from 6 to 18 months of age, when there was no significant gender difference in calcitonin levels.

Regarding historical controls, the applicant has limited in house data. C-cell carcinoma was found in 4/50 controls in the 'non-pivotal' carcinogenicity and in 6/48-control males (18 months old) in the 52 weeks mechanistic study. Published information, although relatively old, shows that the C-cell tumour incidences varied widely in Fischer rats, with incidences up to 12% in males. Thus, the incidence in the LD and HD groups of the pivotal study, which differed significantly from controls, is within that reported in other control groups. In addition, there was no increase of C-cell carcinomas in females or in males in the non-pivotal study.

- Reproductive and developmental studies

Since this application concerns treatment of postmenopausal women only, these data are not essential for the current application. Nevertheless, studies were conducted in rats (covering all reproductive phases) and rabbits (segment II). There were no effects on male fertility. Overall, impaired bone development was the main finding after exposure in utero and /or via milk. It cannot be excluded that these findings have relevance for humans. Thus, strontium ranelate should not be administered during pregnancy. Strontium is accumulated in rat milk, and F1 pups had 2-fold higher plasma levels after suckling, than treated dams. Thus, breast-feeding women should not use strontium ranelate.

- Other toxicity studies

Impurities

The impurity profile of the drug substance proposed for registration has been adequately qualified in nature and limits

Photosafety

Strontium ranelate was found to absorb light in the ultraviolet wavelength range. However, no distribution in eye and skin was demonstrated, and data from an in vitro phototoxicity test showed that strontium ranelate has no phototoxic potential.

Immunotoxicity

A specific study, made in accordance with the Note for Guidance on Repeated Dose Toxicity (CPMP/SWP/1042/99 corr.), supported that strontium ranelate has no immunotoxic potential.

Environmental risk

Environmental risk has been addressed partly, and studies are ongoing to address the areas outlined in the current Note for Guidance on environmental risk assessment. They will be submitted when available. Nevertheless, the lack of these studies does not preclude a recommendation of a positive opinion.

- Summary of salient findings

Single-dose toxicity studies in rodent, dog and monkey given oral or i.v. doses revealed no treatment-related toxicity except for some emesis in monkeys. Thus, strontium ranelate has a low acute toxicity.

Information on long-term effects was obtained in repeat dose toxicity studies in rats, mice and monkeys. The main findings were dose related bone and tooth toxicity, due to exaggerated pharmacological effects.

Additional effects included clinical signs, certain changes of plasma /urine parameters, urinary stones in mice, corneal proliferative vascular changes in one rat carcinogenicity study. Strontium ranelate did not cause a detectable imbalance of Ca or phosphorous homeostasis or of hormones regulating these systems in animals.

In the mouse carcinogenicity study, there was no indication of a treatment related increased tumour incidence. In the rat carcinogenicity study, statistical analyses of neoplastic lesions showed a difference in the incidence of thyroid C-cell carcinomas in males only.

A complete set of reproductive /developmental toxicity studies have been performed. There were no effects on male fertility. Overall, impaired bone development was the main finding after exposure in utero and /or via milk.

Discussion on the non-clinical aspects

Pharmacology: *In vitro*, strontium increased bone formation in certain pre-osteoblastic cell systems, and inhibited the bone resorption activity of osteoclasts. Strontium acted as a full agonist at the CaR expressed in non-bone cells, with lower affinity than Ca. *In vitro*, effects generally occurred at 1 – 20 mM strontium. If these concentrations are relevant for the *in vivo* situation is uncertain. Moreover, strontium's mechanism of action is not known. *In vivo*, long-term dosing of OVX rats and monkeys with strontium ranelate resulted in increased bone formation, but only non-significant trends of reduced bone resorption. In rats, certain positive effects (*e.g.* on bone mass) were seen but increased resistance was only observed at the highest dose tested for 52 weeks in the 'prevention' study design. In OVX monkeys, there were no meaningful effects on bone mass, or bone strength. Moreover, the monkey data do not provide consistent support for the claimed dual effects of strontium on bone remodelling *i.e.* increased bone formation and inhibition of bone resorption. Safety pharmacology studies revealed no major cause for concern.

Pharmacokinetics: From a safety point of view, data on distribution and potential tissue accumulation are of importance. It has been demonstrated that strontium is predominately distributed into calcified tissues, with at least 400 x higher levels compared with blood. No accumulation was identified in non-calcified tissues, while there is insufficient data in animals to conclude whether bone strontium levels reach a plateau during long-term treatment or not.

With respect to **toxicology**, the main findings were dose related bone and tooth toxicity, due to exaggerated pharmacological effects. Bone toxicity was seen only at bone strontium content above 5%, which is 2-3 x higher than the claimed exposure of bone at the intended clinical use, or less than 2x higher than the highest bone strontium content seen after 5 years treatment (3.1%). This margin is narrow, but if such levels may be reached the intended clinical use should be assessed based on clinical data.

There is no indication that the risk for bone toxicity increases with treatment duration per se, as long as the BSC is below that causing bone toxicity. However, since the non-clinical studies have not shown that a plateau for bone strontium content is reached, it is not possible to estimate the risk for bone adverse effects after very extensive treatment duration. This should be further considered from a clinical point of view. The bone strontium content and their association with toxicity are reflected in the SPC (section 5.3).

Carcinogenicity: It cannot be completely excluded that a subtle increase in plasma cation levels may have, in some individuals, affected the progression of thyroid C-cell hyperplasia /adenoma to carcinoma. However, taking the totality of the data into account, there is no clear evidence that the finding of increased incidences of C-cell carcinoma in LD and HD males in the main carcinogenicity study in the rat are related to strontium ranelate treatment. Moreover, there are some differences between human and rat with respect to calcitonin regulation, such as the age-related increased increase in calcitonin in rats, whereas the opposite occurs with increasing age in humans, which indicate that the tumour findings are of minor clinical relevance

4 Clinical aspects

Introduction

Osteoporosis is a systemic skeletal disorder characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility. The clinical consequences of osteoporosis are vertebral and peripheral fractures. Postmenopausal osteoporosis affects women after menopause and results from an accelerated rate of bone loss mainly due to estrogen deficiency. Thus, there is an increase in bone turnover, a decrease in bone mass and bone mineral density. The bone loss is more accelerated during the first years after menopause, and thereafter continues at a slower rate for the lifetime. A variety of different therapies are used for the treatment and/or prevention of postmenopausal osteoporosis: antiresorptive substances (calcitonin, bisphosphonates, 17beta-estradiol, selective oestrogen-receptor modulators) and substances stimulating bone formation (PTH, fluoride).

There is considerable and recent European regulatory experience with the evaluation of medicinal products for the treatment and/or prevention of postmenopausal osteoporosis. In these evaluations, the requirements outlined in the CPMP Note for Guidance on postmenopausal osteoporosis in women (CPMP/EWP/552/95 rev. 1) have been reasonably consistently applied.

Protelos contains strontium ranelate (also referred to as S12911), a molecule comprised of two atoms of stable strontium (Sr) and one molecule of ranelic acid (RA). Strontium ranelate dissociates at the gastro-intestinal level. Strontium is a cation chemically and physically closely related to calcium (Ca). Ranelic acid is an organic, highly polar molecule without pharmacological activity. Strontium is a bone-seeking element and the mode of action is claimed to be through dual effects on bone metabolism, by increased bone formation and decreased bone resorption.

Protelos is indicated for treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.

The recommended daily dose is one 2 g sachet once daily by oral administration. Protelos is intended for long-term use. Protelos should be administered at bedtime, preferably at least two hours after eating, since the absorption of strontium ranelate is reduced by food intake. The product can be taken on an empty stomach.

No dose adjustment is recommended in relation to age, even in the very elderly. No dose adjustment is recommended in patients with mild to moderate renal impairment, while Protelos should not be used in patients with severe renal impairment. No dose adjustment is required in patients with hepatic impairment. Efficacy and safety have not been established in children and adolescents and paediatric use is not recommended.

Pharmacokinetics

The pharmacokinetics of strontium (Sr) as well as ranelic acid (RA) was described in the dossier. Studies were performed in healthy young men and post-menopausal women, the target population. Sr is similar to calcium and is available endogenously with plasma levels in the range 0.030-0.050 mg/l. Ranelic acid is an organic, highly polar molecule. Sr concentrations in plasma and urine were measured by different methods (AAS, ICP-AES and ICP-OES). Ranelic acid concentrations in plasma and urine were measured by HPLC-UV. Validation results were presented for each study and were satisfactory.

- Absorption – Bioavailability

The absorption of Sr is dose-dependent and a less than proportional increase in C_{max} and AUC is observed over a dose range of 0.25 to 8 g. T_{max} occurs between 3 and 5 hours. C_{max} after a 2 g single dose is approximately 6 mg/l. The dose dependency is reasonably caused by the involvement of active, vitamin D-dependent processes in the absorption, as for Ca. The absolute oral bioavailability of Sr from the 2 g sachet formulation for marketing is 27% (CV 22%) in healthy young males and a population pharmacokinetic analysis combining data from different studies indicated a similar figure (25%) in healthy postmenopausal women. Throughout the product development, different formulations have been used and bioequivalence studies of adequate design were performed to compare formulations. The final formulation for marketing was used in the pivotal Phase III trials and in many pharmacokinetic studies.

The organic moiety, ranelic acid, shows irregular and variable absorption, probably due to its high polarity. The absolute oral bioavailability is about 2.5%.

As could be expected, both food rich in Ca and Ca alone decrease the absorption of Sr and the effect was most pronounced with the combination of food and Ca (F_{Rel} 29%). The food tested did not have a low Ca content, and therefore the effect of food *per se* could not be evaluated. The breakfast served did not have a high fat content, which is normally used for assessment of food effects on absorption. The effect of food and Ca has not been studied with the formulation for marketing, but since bioequivalence has been established between different formulations this is not deemed a problem. It can be concluded that there is a substantial effect of food and Ca. In the clinical studies there was no restriction with respect to dosage in relation to food intake. Since the absorption is optimised when Protelos is administered 2-3 hours after food and or Ca intake, the SPC states that drug administration should preferably be at least two hours after a meal and also clarify that food/Ca should be avoided a time after Protelos intake.

- Distribution

The volume of distribution (V_{ss}) of Sr is 64 ± 15 litres and the plasma protein binding is moderate (25%). V_{ss} for RA is about 13 litres and the plasma protein binding is 27%.

Strontium is dose dependently deposited preferentially into newly formed bone as determined by various methods from biopsies of postmenopausal women with established osteoporosis following treatment with strontium ranelate over a period of 2 years (STRATOS) and 3 years (Phase III population). The strontium concentration in bones increased non-linearly.

- Elimination

Sr is an ion partly eliminated by renal excretion ($47 \pm 6\%$). Plasma CL was estimated to 12 ml/min and renal CL was about 7 ml/min. Half the dose is excreted in urine and no metabolism occurs. The remainder seems to be eliminated by gastrointestinal secretion and by slow release from bone tissues. The effective half-life appears to be 50-60 hours, based on the time taken to reach steady state.

IV administered ranelic acid is mainly eliminated renally ($84 \pm 16\%$) with total and renal CL of 78 ml/min and 62 ml/min, respectively. The half-life is approximately 3 hours. Oral administration of radiolabelled S12911 indicates poor absorption of ranelic acid. From presented *in vitro* and *in vivo* data there are no indications of metabolism, which is expected due its polar and acidic properties.

- Dose proportionality and time dependencies

There is a dose dependency in the absorption of Sr, with a less than proportional increase in exposure with increasing dose. This is likely to be due to saturation of an active absorption process very similar to that of calcium.

An accumulation ratio for Sr of about 9 was observed in postmenopausal females when comparing AUC_{0-10h} after the first dose and at steady state. The applicant made a comparison between $AUC_{0-\infty}$ after a single dose from one study and AUC_{0-10h} at steady state from another study and the estimates were rather similar. Thus, the pharmacokinetics of Sr appears to be time independent. The estimated terminal half-life of Sr was longer after repeated dosing compared with single dose studies (about 200 hours compared with 60-100 hours). The half-life probably reflects redistribution from bone and an effective half-life of about 60 hours has been suggested. Steady state for Sr seems to be reached within 2-3 weeks and no apparent changes over time have been observed.

- Special populations

Plasma Sr data were collected in the two pivotal Phase III studies involving post-menopausal women treated for osteoporosis and the influence of co-variates on Sr pharmacokinetics was investigated.

Creatinine clearance was found to be the most important source of variability on Sr levels. The creatinine clearance was shown to induce a 30% increase in strontium levels when it varied from 70 to 30 ml/min. A similar effect of renal impairment was observed in a Phase I study.

Severe renal impairment has not been studied. In the SPC, it is recommended that Protelos should not be used in patients with severe renal impairment in the absence of bone safety data. No dose adjustment is recommended for mild to moderate renal impairment. This is acceptable, since the mean

creatinine clearance in the Phase III trials was about 50 ml/min, and thus, the efficacy and safety of Protelos has been established in a population with mild to moderate renal impairment.

No study has been conducted in patients with hepatic impairment, but due to the pharmacokinetic properties of Sr an effect is not expected. From the population pharmacokinetic analysis, age and weight had no effect on Sr CL.

From the population pharmacokinetic analysis, age and weight had no effect on Sr CL. There was no study in patients with hepatic impairment. Postmenopausal females tend to have somewhat higher bioavailability of Sr compared with young, healthy males.

- Interaction studies

In vitro metabolism studies were conducted to assess the potential for Sr to inhibit different cytochrome P450 isoenzymes. No effect on any of the studied CYPs was observed, although the highest Sr concentrations studied were relatively low compared with steady state *in vivo* plasma levels.

In vivo interaction studies have been performed with the antacid Maalox[®] and with Vitamin D supplementation. In addition, interactions with co-administered drugs were investigated in a Phase III population pharmacokinetic analysis. Vitamin D supplementation had no effect on the pharmacokinetics of Sr. Administration of Maalox[®] 2 hours after S12911 caused a 14% decrease in AUC (90% CIs within 80-125%), while administration 2 hours before or together with S12911 caused 20-25% decreases. When S12911 and an antacid like Maalox[®] are co-prescribed, the preferred dosing regimen would be to administer the antacid 2 hours after S12911 to achieve the highest bioavailability. However, when this dosing regimen is impractical due to the recommended administration of Protelos at bedtime, concomitant intake remains acceptable.

It can be concluded that few interaction studies have been performed with S12911 and other drugs. Since Sr and RA are not metabolised and no *in vitro* inhibitory potential was observed for Sr on CYP isoenzymes, interactions involving absorption are most likely to occur. Food, Ca and the antacid Maalox[®] reduced the bioavailability of Sr to different extents.

No study has been conducted to evaluate the effect of S12911 on the absorption of other drugs. Divalent cations like Ca and Sr can form complexes with e.g. tetracycline and quinolone antibiotics administered orally and thereby reduce their absorption. In the absence of specific interaction data for S12911, a restrictive wording in the SPC for Protelos is included, (to discontinue Protelos treatment during the period of antibiotic use).

Pharmacodynamics

- Mechanism of action

The applicant proposes that Sr acts on bone through dual mechanisms of inhibition of resorption by osteoclasts and maintenance or stimulation of bone formation by osteoblasts.

- Primary and secondary pharmacology

The sum of data from *in vitro* and *in vivo* (rat and cynomolgus) preclinical and human (biochemical markers, BMD, histomorphometry) studies presented by the applicant provide evidence compatible with modest effects of Sr on bone remodelling dynamics in the direction of reduction of bone turnover at tissue level (reduced activation frequency of remodelling units) together with maintenance or, possibly, slight stimulation of bone formative activities at the cellular level.

This chain of events presumes a degree of “de-coupling” of the otherwise tightly linked resorption-formation sequence of adult bone remodelling. The exact mechanisms through which this would take place are not known. It would appear logical to presume a combination of systemic effects through reduced parathyroid hormone secretion secondary to the increased 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 MAH 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 Δ BMD 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 Δ BMD 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

- Dose response study (ies)

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, double blind, placebo-controlled, 24 month 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.

- Main study (ies)

Treatment of postmenopausal osteoporosis

The indication claimed for treatment of postmenopausal osteoporosis is based primarily on 36-month data from two, still ongoing five-year trials, **SOTI** and **TROPOS**. Both are European multi-centre studies, performed as double blind trial testing Sr ranelate 2 g/d vs. placebo in elderly Caucasian women on individually titrated calcium and vitamin D supplementation, which was achieved within a common run-in protocol (FIRST). Generally, both trials are well presented and are considered adequately designed, executed and analysed. Within-study retention of patients was acceptable considering study duration and the elderly or very elderly population included

Altogether 9,196 Caucasian women >50 years old (mean age 74 ± 7 years, no upper age limit), postmenopausal for >5 years (mean 26 ± 9 years) and “presenting severe osteoporosis” were enrolled. More specifically,

- Women <70 years should have a history of osteoporotic vertebral fracture

- Women 70-74 years should have a history of osteoporotic vertebral fracture or at least one additional risk factor for fracture, such as:
 - personal history of osteoporotic fracture (vertebral or peripheral) post menopause, or
 - resident in retirement homes or
 - frequent falls (more than 4) / year or
 - maternal history of osteoporotic fractures (hip, vertebrae, wrist)
- All women should be ambulant (*i.e.*, able to walk alone) and have a life expectancy of more than 4 years.

Exclusion criteria were generally typical of osteoporosis treatment trials and included:

- Significant liver or kidney disease (S-creatinine >140 µmol/l), hypercalciuria
- Other skeletal disease, hyperthyroidism
- Chronic systemic glucocorticoids, antiepileptics, phosphate binders
- Recent osteoporosis therapy

SOTI (N = 1,649, mean age 69.7 years) focused on patients with prevalent vertebral fracture. According to central grading, this was verified in 87.5% of patients at baseline. In 90.1% there was a history of axial or peripheral osteoporotic fracture. Baseline lumbar or femoral BMD T-score <-2.5 was present in 87.5% and 64.9%, respectively.

Results

The **primary efficacy analysis** was the incidence over time of patients with new vertebral fracture until 36 month ITT/FAS (Genant semi-quantitative grading, centralised reading). This is in compliance with CPMP NfG. Benefit of Sr ranelate vs. placebo was noted from 12 month onwards. Thirty-six month data for the primary analysis are summarised in the table below.

Incidence over time of patients with at least one new vertebral fracture and relative risk in the FAS (semi-quantitative assessment)

Table 1: Incidence of patients with vertebral fracture and relative risk reduction

	Placebo	PROTELOS	Relative Risk Reduction vs. placebo (95%CI), p value
SOTI	N=723	N=719	
New vertebral fracture over 3 years	32.8%	20.9%	41% (27-52), p<0.001
New vertebral fracture over the 1 st year	11.8%	6.1%	49% (26-64), p<0.001
New clinical vertebral fracture over 3 years	17.4%	11.3%	38% (17-53), p<0.001

Pre-specified sensitivity analyses supported the primary analysis. A *post hoc* robustness assessment was performed, using various assumptions for outcome for randomised patients (n=207) initially excluded from FAS (nine untreated patients and 198 patients with less than two assessable X-rays between month 0 and month 36). Except for the most conservative maximal bias assumption (100% fractures in active groups, 0% in placebo), this indicated retained significant effects of Sr.

Outcomes in the population with osteoporotic baseline Bone Mineral Density (BMD) (RR = 0.63) and PP (RR = 0.59-0.62) were consistent with the primary analysis, as were results for new clinical

vertebral fracture, new or worsening vertebral fracture, and new vertebral fracture by quantitative morphometry.

Consistent with the effect on vertebral fracture, there was significantly less mean loss of height in the Sr ranelate group, compared with placebo (-7 ± 13 mm and -9 ± 14 mm, respectively, $p=0.006$).

There was no discernible effect on the incidence of patients with new non-axial, osteoporosis-related fracture (RR = 0.91 [0.71; 1.18]).

Lumbar BMD (non-adjusted) increased on average 14.4% on Sr ranelate vs. placebo. Bone Turnover (BTO) marker profiles bone Alkaline Phosphatase and Type I collagen C-telopeptide cross links (bALP and serum CTX) showed a trend to increase over time in both treatment groups, after a transient dip in mean serum CTX in the Sr ranelate group. Mean levels of bALP were higher and of CTX lower on Sr ranelate, compared with placebo at all time points, however.

TROPOS (N = 5,091, mean age 76.8 years, range 55-100 years, 61.6% ≥ 75 years) focused on patients with femoral osteoporosis. Baseline femoral BMD T-score < -2.5 (Applicant's reference) was verified for 89%. A history of fragility fracture (axial or peripheral) was present in 55%.

The **primary efficacy analysis** was incidence over time of patients with at least one incident osteoporosis-related peripheral fracture (ITT/FAS), using Kaplan-Meier method and unadjusted Cox model for inference. The analysis was carried out on available data up to the cut-off date (last patient past 36 month and including retrieved data for dropouts), and considering all information about peripheral fracture occurrence up to 6 months after last treatment intake. Vertebral fractures were analysed secondarily, using the same criteria as in SOTI

The focus on (all) peripheral osteoporosis-related fractures reflects advice in 1994 FDA guidelines. CPMP Note for Guidance on postmenopausal osteoporosis in women (CPMP/EWP/552/95 rev. 1) does not exclude this primary outcome measure, but also identifies proximal femur as the non-axial fracture site of key importance for a therapeutic claim.

Over three years, incident peripheral osteoporosis-related fracture was recorded in 233 patients on Sr ranelate, compared with 276 on placebo (RR ITT/FAS = 0.85 [0.71;1.01]). Analyses in patients exposed for at least six months and in patients compliant according to blood Sr levels were nominally significant, as was analysis for predefined major osteoporosis-related fractures, indicating a pharmacological effect of therapy. In response to CPMP LoQ, the applicant presented the same analysis at four years, based on 286/341 patients with fracture: RR=0.83 [0.712;0.975]

Proximal femur fracture (for which the trial was not dimensioned) occurred during the first three years of therapy in 62 patients on Sr ranelate, compared with 74 on placebo (RR = 0.85 [0.61;1.19], $p=0.33$). Also for this fracture site nominal significance was achieved in the subset of patients compliant according to blood Sr levels (RR = 0.59 [0.37; 0.95]).

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. The CPMP asked the applicant to present data also for the subset with established osteoporosis (*i.e.* BMD T-score < -2.5 and prevalent fragility fracture). In response to the request and based on *a posteriori* analysis, the applicant proposes a revised target population for hip fracture prevention: women ≥ 74 years and with femoral BMD T-score < -3 (< -2.4 NHANES III). The CPMP agreed that there is internal and external support for the relevance of such a population cut, which represented 42% of patients randomised to TROPOS and that therapeutic indications have been approved for the bisphosphonates alendronate and risedronate, based on similar subgroup and/or *post hoc* analyses. In this subset and based on 32 and 51 upper femur fractures in Sr ranelate and placebo groups, respectively, nominally significant efficacy of Sr ranelate was seen: RR = 0.64, [0.412;0.997]. Additional analyses from four-year follow-up in the targeted population (RR = 0.69) and from three years in the whole TROPOS subset fulfilling the revised BMD criteria (RR = 0.70) indicate consistency.

For vertebral fractures_TROPOS provided corroboration of SOTI. Relative risks for new vertebral fracture were RR = 0.61 [0.51; 0.73] (overall), RR = 0.68 [0.53; 0.85] (patients with prevalent vertebral fracture) and RR = 0.55 [0.42; 0.72] (patients without prevalent vertebral fracture).

Findings for BMD and BTO markers were qualitatively similar to those in SOTI. For BTO markers (bALP and U-NTX), mean levels increased over time in both treatment groups, but less with Sr ranelate compared with placebo.

- Analysis performed across trials (pooled analyses and meta-analyses)

A prespecified **Integrated Analysis of Efficacy (IAE)** was submitted for three-year data, corresponding to an analysis of pooled individual data of SOTI and TROPOS, *i.e.* on a total of 6,551 patients (3,295 in the Sr ranelate group, 3,256 in the placebo group). In the IAE, the statistical analyses were performed with similar methods as those described for princeps analyses in the SOTI and TROPOS studies, complemented by an adjustment on a fixed study effect (Cox model and covariance analysis). Homogeneity of treatment effect across studies was studied using the treatment-by-study interaction. Meta-analytic methods on summary statistics were used as sensitivity analyses. Additional subsets of patients ≥ 80 years and patients with baseline osteopenia were identified. For vertebral fractures, the IAE, as expected, contributed mainly a slight improvement of the precision of the estimate for RR. The analysis also provided evidence of efficacy of Sr ranelate for patients ≥ 80 years (N = Sr/placebo: 443/452), RR = 0.68 [0.50;0.92] and for patients with baseline BMD in the osteopenic range (N = Sr/placebo: 206/203), RR = 0.38 [0.21;0.71].

A posteriori analysis of data from patients (N=176) with baseline lumbar spine and/or femoral neck BMD in the osteopenic range, no prevalent fracture and at least one additional risk factor for fracture was performed. It was shown that PROTELOS reduced the risk of a first vertebral fracture by 72% over 3 years (incidence of vertebral fracture 3.6% with strontium ranelate vs. 12.0% with placebo) in the analysed patients population.

For peripheral osteoporosis-related fractures, the IAE was performed on the FAS peripheral data sets (until endpoint) from SOTI and TROPOS and identified 331 patients with new fracture out of 3,295 in the Sr ranelate group, compared with 389/3,256 on placebo. This corresponds to RR = 0.85 [0.74; 0.99], (p = 0.033, study-adjusted Cox model). A meta-analytic approach confirmed this result (p = 0.031). The effect appeared somewhat enhanced in the PP compliant according to blood Sr levels (RR = 0.74 [0.62; 0.89], study adjusted Cox model; p = 0.001). Neither clinically relevant, nor statistically (p = 0.853) significant treatment*study interaction was detected.

- Clinical studies in special population: (see also Pharmacokinetic)

The general safety profile of strontium ranelate in patients presenting a creatinine clearance below 30 ml/min was similar to that described in the overall Phase III Safety Set. However, the effects of severe renal impairment are known to be potentially deleterious on bone. As no bone safety data are available in patients with severe renal insufficiency (creatinine clearance below 30 ml/min) treated by strontium ranelate, a statement is included in section 4.4 of the SPC.

- Discussion on clinical efficacy

Treatment of postmenopausal osteoporosis

The efficacy claims were based primarily on 36-month analyses on incidences of patients with new fracture from two, large, 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.

SOTI provided robust evidence of efficacy of Sr ranelate 2 g/d to reduce the risk of new vertebral fracture in a population characterised by established postmenopausal osteoporosis, at high risk of recurrent vertebral fracture. The magnitude of effect appears comparable with that achieved with bisphosphonates in similar populations.

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 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 risk 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.

In an a-posteriori analysis of patients from the pooled SOTI and TROPOS studies with baseline lumbar spine and/ or femoral neck BMD in the osteopenic range and without prevalent fracture but with at least one additional risk factor for fracture (N=176), PROTELOS reduced the risk of a first vertebral fracture by 72% over 3 years (incidence of vertebral fracture 3.6% with strontium ranelate vs. 12.0% with placebo). Even if the findings refer to *post hoc* analysis and to a small subset of the study population, additional analyses of different population cuts presented with the applicant's response support their relevance, and it is considered acceptable to mention these data in the pharmacodynamic section of the SPC.

Clinical safety

- Patient exposure

In all, 4,138 subjects were exposed to Sr ranelate during the clinical development. Of these, 3,790 were participants in Phase II and III trials. If duration of exposure is defined as time from date of first intake to date of last intake (or withdrawal), subtracting interruption periods, some 2,600 patients were exposed to Sr ranelate for at least 12 months and 1,400 patients for at least 36 months, respectively.

Discussion of safety data focuses on the Phase III data set, which provides long-term information on outcome with the applied / highest tested dose, 2 g/d. Important subsets from Phase III are patients ≥ 80 years (N = 1,528) and patients with $Cl_{creat} < 30$ ml/min (N = 426), as these involve individuals with higher average exposure to Sr and/or higher anticipated degree of frailty.

- Adverse events

Overall incidence rates for adverse events with strontium ranelate did not differ from placebo and adverse events were usually mild and transient. The most common adverse events consisted of nausea and diarrhoea, which were generally reported at the beginning of treatment with no noticeable difference between groups afterwards. Discontinuation of therapy was mainly due to nausea (1.3% and 2.2% in the placebo and strontium ranelate groups respectively).

Adverse reactions, defined as adverse events considered at least possibly attributable to strontium ranelate treatment in phase III studies are listed below

Table Emergent adverse events under treatment considered as possibly in relation with the treatment intake

PT	EAE				SEVERE EAE				EAE RESULTING IN TRT DISCONTINUATION				SERIOUS EAE				TRT-RELATED EAE			
	S12911 (N=3352)		Placebo (N=3317)		S12911 (N=3352)		Placebo (N=3317)		S12911 (N=3352)		Placebo (N=3317)		S12911 (N=3352)		Placebo (N=3317)		S12911 (N=3352)		Placebo (N=3317)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Nausea	222	6.6	142	4.3	14	0.4	4	0.1	82	2.4	47	1.4	1	<0.1	2	0.1	12	3.8	67	2.0
Diarrhoea NOS	219	6.5	154	4.6	25	0.7	9	0.3	61	1.8	28	0.8	1	<0.1	1	<0.1	98	2.9	54	1.6
Loose stools	36	1.1	6	0.2	3	0.1	-	-	6	0.2	2	0.1	-	-	-	-	19	0.6	3	0.1
Headache NOS	101	3.0	79	2.4	11	0.3	6	0.2	17	0.5	8	0.2	1	<0.1	1	<0.1	29	0.9	15	0.5
Dermatitis NOS	69	2.1	54	1.6	2	0.1	2	0.1	3	0.1	3	0.1	2	0.1	-	-	6	0.2	5	0.2
Eczema NOS	50	1.5	40	1.2	1	<0.1	1	<0.1	1	<0.1	1	<0.1	-	-	-	-	6	0.2	2	0.1
Dermatitis allergic	33	1.0	18	0.5	5	0.1	2	0.1	5	0.1	2	0.1	1	<0.1	1	<0.1	7	0.2	4	0.1

PT = Preferred term

EAE = Emergent Adverse Event

TRT = Treatment

N = number of patients

n = number of patients with at least one EAE under treatment considered as possibly in relation with the treatment intake

%. $[n/N] \times 100$

An analysis of emergent AEs by SOC provided additional information.

AEs involving the following SOC were more frequently reported in the Sr ranelate group than in placebo (between-group difference of at least 0.5%):

- Gastrointestinal disorders: 40.4% of the patients in the Sr ranelate group versus 39.2% in the placebo group; E (SE) = 1.2 (1.2)% [-1.2; 3.5]
- Vascular disorders: 26.3% of the patients in the Sr ranelate group versus 24.4% in the placebo group; E (SE) = 1.9 (1.1)% [0.7; 4.0],
- Nervous system disorders: 20.9% of the patients in the Sr ranelate group versus 18.9% in the placebo group; E (SE) = 2.0 (1.0)% [0.1; 3.9],

AEs within SOC gastrointestinal disorders referred mainly to terms *nausea*, *diarrhoea* and *loose stools*, reported more frequently with Sr ranelate, compared with placebo. There were no obvious signals for more serious events the applicant has provided an adequate appraisal, further detailed in the clinical part of the assessment. Overall, it appears well established that treatment with Sr ranelate is associated with common ADRs of gastrointestinal intolerance. Although mainly mild to moderate, these types of adverse events caused the majority of premature discontinuations in clinical trials.

- Serious adverse event/deaths/other significant events

Within SOC vascular disorders, there was a worrying, increased reporting rate with Sr ranelate specifically for terms related to embolism and thrombosis. A special search for AEs of thrombosis revealed a significantly increased reporting rate for patients on Sr ranelate vs. placebo (3.3 vs. 2.2%, difference 1.1% [0.4; 1.9]).

A medical review was performed and showed a statistically significant increase in reports of emergent venous thromboembolism (VTE) in patients on Sr ranelate (OR = 1.5 [1.1; 2.1] at three years). The point estimate for OR was unchanged when focusing on patients with VTE emergent under treatment. For pulmonary embolism (PE), the excess risk was similar (OR = 1.7 [1.0; 3.1]). Six pulmonary embolisms (PE) led to death in the Sr ranelate group vs. 3 in the placebo group and 7 led to treatment discontinuation in the Sr ranelate group, vs. 3 in placebo. Among the VTE emergent under treatment, PE was reported as serious adverse event for 25 patients in the Sr ranelate group vs. 14 in placebo. In

≥80-year-old patients, “pulmonary embolism, thrombosis and stenosis” was reported by 12 patients in the Sr ranelate group vs. 3 in placebo.

Increased reporting of embolism, thrombosis and stenosis in patients on Sr ranelate was seen also in the large subsets of patients treated concomitantly with oral anticoagulants or antiplatelet agents, respectively. An exploration of predisposing factors failed to disclose any imbalances between groups.

In response to CPMP LoQ, the applicant presented comprehensive additional *in vitro* and clinical data aiming to elucidate any mechanistic relationship between Sr exposure and effects on haemostasis. These efforts are acknowledged as relevant, but have not produced any explanation. Four-year data from the ongoing trials indicate a largely unchanged increased risk for VTE in Sr ranelate-treated patients. It is noted that the risk increase appears less than that seen with SERM and HRT. The SPC reflects this concern within section 4.4. The applicant has submitted a relevant pharmacovigilance plan, detailing how this issue will be addressed within ongoing large-scale extension to pivotal trials and within post-marketing pharmacovigilance activities

For AEs within SOC nervous system disorders, the following could be noted:

Headaches all forms were significantly more common with Sr ranelate (3.9% vs. 2.9%, difference 1.0% [0.1; 1.9]). These were mostly mild to moderate. Of more concern, there were discrete but consistent increases in reporting rates for a number of other symptoms and signs in patients on Sr ranelate, such as *disturbances in consciousness, amnesia, memory loss, seizures, “encephalopathies”*. Overall, between-group differences for AEs within SOC nervous system disorders appeared enhanced in patients ≥80 years and in patients with $Cl_{creat} < 30$ ml/min.

Response to CPMP LoQ provided additional data up to four years, which were similar to the more short-term findings previously submitted. Other analyses failed to provide specific explanation for the observations, which are presented in the SPC, section 4.8. Further focused surveillance will be conducted within ongoing extension trial and post-marketing. This is acceptably detailed in the submitted pharmacovigilance plan

The Phase III data set did not provide indications of increased risk of mortality in patients treated with Sr ranelate (RR = 0.94 [0.77; 1.19]). It is noted, however, that patients on Sr ranelate were nominally over-represented among those dying from disorders that could be related to thrombosis / embolism (including PE and fatal cerebrovascular accident, intestinal infarction). There was also an increased death rate among actively treated patients due to cardiac disorders during the first year of study, but not overall.

- Laboratory findings

Strontium exposure and effects on phosphocalcic homeostasis

Chronic treatment with Sr ranelate 2 g/d is associated with steady-state blood Sr levels around 120-140 µmol/l, which, as expected, are further moderately increased in patients with significant renal impairment. It has been acceptably shown that there is no progressive increase over time in these circulating levels. As detailed in the clinical assessment, there are secondary effects on blood calcium and phosphorus levels in the direction of hypocalcaemia and hyperphosphataemia, respectively, reasonably secondary to calcimimetic activity of Sr on parathyroid gland. Abnormally low serum calcium was noted at some time in 45% of patients on Sr, compared with 15% on placebo. There were no adverse events related to hypocalcaemia.

No relevant safety concerns were raised for measured levels of calcitonin, 25 (OH) vitamin D or 1,25 (OH)₂ vitamin D, respectively.

Strontium tissue accretion

New animal data, provided with the response to CPMP LoQ gave reassurance that chronic ingestion of Sr may not be associated with deposition in non-calcified tissues. In humans, the only tissue data available are those from iliac bone biopsies performed in Phase II and III. The applicant proposed that these indicate that a plateau is reached after 36 months on therapy. As detailed in the clinical assessments, the basis for this proposal appears weak and further long-term biopsy data are necessary to provide reassurance that levels similar to those associated with mineralisation defects in preclinical models are not reached. Within the submitted pharmacovigilance plan, the applicant commits to continued efforts to provide such biopsies from M72-M96 of ongoing extension trial. Off-therapy data over 12

months for BMD were presented for a subset of patients previously treated for 24 months in Phase II trials. The contributions to loss of BMD off-therapy of release of Sr and loss of “true” bone mineral, respectively, are uncertain.

Bone histomorphometry

In similarity with other recent applications in the therapeutic area, the dossier for Protelos provides only sparse long-term histomorphometric data for assessment of pharmacodynamic effects and bone safety. The findings are discussed in detail in the clinical assessment. No safety concerns were raised.

ECG and vital signs

An effect of Sr on cardiac conduction could be conceived. However, adequate preclinical studies failed to identify any impact of Sr on repolarisation. In Phase III studies, ECGs were recorded and read centrally in a subset representing approximately 10% of randomised patients. Analyses focused on post-baseline data under treatment. The findings do not give rise to specific concern.

Laboratory AEs

A relevant selection of biochemistry and haematology parameters were analysed in clinical trials.

For biochemistry parameters not discussed in relation to phosphocalcic homeostasis, the only noticeable change observed with Sr ranelate concerned serum Creatine Kinase (CK). Mean CK levels increased from baseline to last value under treatment in both treatment groups. This increase was more pronounced in the Sr ranelate group (31.3 ± 80.8 IU/L) than in with placebo (13.1 ± 46.6 IU/L). Estimated difference E (SE) between groups was of 18.2 (1.7, [14.8; 21.6] IU/L). In all 789/2680 patients (29.4%) in the Sr ranelate group and 475/2705 patients (17.6%) in the placebo group switched at least once from a baseline value within the reference range to a CK value above ULN. Normalisation of elevated CK during treatment with Sr ranelate was assessable in 599 patients. Normalisation under treatment occurred in 86.0% of these patients (n = 515). Phase II data indicated a clear dose relationship for mean CK elevation during treatment with Sr ranelate. All isoenzyme analyses suggested that CK elevation was explained by elevation of CK MM.

Muscular symptoms, mainly muscle cramps and night cramps were reported by 5-6% of patients with CK elevation, with similar incidence between groups.

No relevant changes were seen for haematology parameters.

The mechanism behind the dose-related effect of Sr on skeletal muscle cell integrity remains unclear. Additional analyses provided in response to LoQ indicate that the finding may be innocuous. No additional concerns were raised in patients at increased exposure (the very old and renally impaired), or in patients on concomitant statin or fibrate. Additional data will become available from final phases of ongoing controlled trials and from long-term OL extension to these. Mechanistic studies using a non-ischaeamic arm exercise model are ongoing and will be provided according to agreed timelines.

- Discussion on clinical safety

The safety profile has been well illustrated in a large population of elderly and very elderly patients treated long term with Sr ranelate 2 g/d. Additional, controlled safety data will be provided from ongoing phases of these trials. At this stage, the following is concluded:

- Treatment with Sr ranelate is associated with an approximately 50% increase in the annual risk for VTE, including PE. This is established during the first year of therapy and appears to remain unchanged thereafter. No explanation has been obtained, despite comprehensive analyses, and no specific risk group has been identified. This finding is acceptably described in the SPC. Further targeted surveillance and analysis will take place, as described in the pharmacovigilance plan.
- Reports of some nervous system disorders were more frequent with Sr ranelate, compared with placebo. Especially, reports of CNS effects such as mental impairment, disturbed consciousness, memory loss/amenia and seizures create some concern. No mechanism has been elucidated. The SPC has been amended and is now considered acceptable in its description of these events. Further targeted surveillance and analysis will take place, as described in the pharmacovigilance plan.

- Sr ranelate is associated with common ADRs of gastrointestinal intolerance, but there are no indications of serious gastrointestinal complications to therapy and these problems are considered clinically manageable.
- There is clear impact of treatment with Sr ranelate on skeletal muscle cell integrity, as expressed by circulating levels of CK. The clinical importance of this may be minor, but surveillance will be needed, as described within the pharmacovigilance plan post-marketing.
- There is some remaining concern regarding any long-term consequences of skeletal accretion of Sr. The applicant has committed to continued attempts to provide additional bone biopsy data from long-term extension to pivotal trials.

5 Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

Non-clinical *in vitro* data indicate that strontium increased bone formation in certain pre-osteoblastic cell systems, and inhibited the bone resorption activity of osteoclasts. However, strontium's mechanism of action is not known. Available *in vivo* studies in OVX animals provide weak support only in terms of efficacy for the intended clinical use. It has been demonstrated that strontium is predominately distributed into calcified tissues. No accumulation was identified in non-calcified tissues, while there is insufficient non-clinical data to assess whether bone strontium levels reach a plateau during long-term treatment. The main toxicological finding was bone and tooth toxicity, which occurred only at bone strontium content above 5%. There is no indication that the risk for bone toxicity increases with treatment duration per se, as long as the BSC is below that causing bone toxicity.

Efficacy

The efficacy claims were based primarily on analyses on incidences of patients with new fracture from two, large, ongoing, 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.

SOTI provided robust evidence of efficacy of Sr ranelate 2 g/d to reduce the risk of new vertebral fracture in a population characterised by established postmenopausal osteoporosis, at high risk of recurrent vertebral fracture. The magnitude of effect appears comparable with that achieved with bisphosphonates in similar populations.

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 risk 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.

Subset analysis of pooled data from treatment trials TROPOS and SOTI indicated that Sr ranelate 2 g/d reduces the risk for new vertebral fracture in elderly postmenopausal women with baseline BMD in the osteopenic range both at lumbar spine and femoral neck. Even if the findings refer to *post hoc* analysis and to a small subset of the study population, additional analyses of different population cuts presented with the applicant response support their relevance, and it is considered acceptable to mention these data in the pharmacodynamic section of the SPC.

Safety

The safety profile has been well illustrated in a large population of elderly and very elderly patients treated long-term with Sr ranelate 2 g/d. Additional, controlled safety data will be provided from ongoing phases of these trials.

Treatment with Sr ranelate is associated with an approximately 50% increase in the annual risk for VTE, including PE. This finding is acceptably described in SPC. Further targeted surveillance and analysis will take place, as described in the pharmacovigilance plan.

Reports of some nervous system disorders were more frequent with Sr ranelate, compared with placebo. Especially, reports of CNS effects such as mental impairment, disturbed consciousness, memory loss/amnesia and seizures create some concern. No mechanism has been elucidated. The SPC has been amended and is now considered acceptable in its description of these events. Further targeted surveillance and analysis will take place, as described in the pharmacovigilance plan.

Sr ranelate is associated with common ADRs of gastrointestinal intolerance, but there are no indications of serious gastrointestinal complications to therapy and these problems are considered clinically manageable.

There is clear impact of treatment with Sr ranelate on skeletal muscle cell integrity, as expressed by circulating levels of CK. The clinical importance of this may be minor, but surveillance will be needed, as described within the pharmacovigilance plan post-marketing.

There is some concern regarding any long-term consequences of skeletal accretion of Sr. The applicant has committed to continued attempts to provide additional bone biopsy data from long-term extension to pivotal trials.

Benefit/risk assessment

The comprehensive clinical programme, and especially the contribution of data in the elderly and very elderly is acknowledged. From the efficacy viewpoint, the submitted documentation is considered sufficiently robust to support an indication for treatment of postmenopausal osteoporosis, to reduce the risk of vertebral and hip fractures, with reference to section 5.1 of the SPC for further information to the prescriber regarding the specifics of the target population. For this indication, the demonstrated effect of Sr ranelate 2 g/d appears comparable with that of bisphosphonates, and the strategy to accept a therapeutic indication partly based on *post hoc* analysis of a revised target population of particular medical interest has regulatory precedent in the European licensing of bisphosphonates.

The applicant has provided a pharmacovigilance plan according to ICH E2E, which has been reviewed by the PhWP and was found to adequately summarise the identified safety concerns, most importantly increased risks for VTE and nervous system dysfunction. These concerns are not considered incompatible with an acceptable benefit/risk ratio. The pharmacovigilance plan provides acceptable strategies for further monitoring and analysis of these and other safety issues.

Recommendation

”Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of Protelos in the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures was favourable and therefore recommended the granting of the marketing authorisation.