EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 April 2013
EMA/PRAC/136656/2013
Pharmacovigilance Risk Assessment Committee (PRAC)

PSUR assessment report

Strontium ranelate

Procedure No.: EMEA/H/C/560/PSU/031 and EMEA/H/C/561/PSU/031

Period covered by the PSUR: 22 September 2011 to 21 September 2012

Note

Assessment report as adopted by the PRAC with all information of a commercially confidential nature deleted.

Following the PRAC recommendation on this PSUR, the Committee for Medicinal Products for Human Use (CHMP) adopted an opinion. This opinion's annex IV "Scientific conclusions and grounds recommending the variation to the terms of the Marketing Authorisations can be found under the Assessment history tab of the EPAR.

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List of abbreviations

AE : Adverse Event
ANSM : Agence Nationale de Securité du Médicament
BMD : Bone Mineral Density
BSA : Blind Safety Analysis
CHMP : Committee for Medicinal Products for Human use
CK: Creatinine phospho-Kinase
CPRD : Clinical Practice Research Datalink
DHPC : Dear Healthcare Professional Communication
DRESS : Drug Rash with Eosinophilia and Systemic Symptoms
DSRU : Drug Safety Research Unit
EAE : Emergent Adverse Event
EC : Expert Committee
EEA : European Economic Area
EMA : European Medicines Agency
FVFP: First Visit First Patient
GP : General Practitioner
GPRD : General Practice Research Database (former name of CPRD)
GVP : Good Pharmacovigilance practices
HCP : Health Care Professional
HES : Hospital Episode Statistics
HLGT : High Level Group Term
HRT : Hormone Replacement Therapy
HSA : Health Sciences Authority
IAS : Integrated Analysis of Safety
IB : Investigator Brochure
IBD : International Birth Date
ICSRs : Individual Case Safety Reports
IHD : Ischaemic Heart Disease
IME : Important Medical Event
IRE : Identified Risk Events
LVLP : Last Visit Last Patient
MA : Marketing Authorization
MAH : Marketing Authorization Holder
MedDRA : Medical Dictionary for Regulatory Activities
MI : Myocardial Infarction
ONS : Office of National Statistics
OSA: Overall Safety Assessment
PAS : Post-Authorization Study
PASS : Post-Authorization Safety Study
PE: Pulmonary Embolism
PIL : Patient Information Leaflet
PMO : Post-Menopausal Osteoporosis
PSP : Patient Support Program
PSUR : Periodic Safety Update Report
PT : Preferred term
PY: Patient-years
PWP : Pharmacovigilance Working Party
RMP : Risk Management Plan
RSI : Reference Safety Information
SAE: Serious Adverse Event
SJS : Stevens-Johnson Syndrome
SmPC : Summary of Product Characteristics
SMQ : Standard MedDRA Queries
SOC : System Organ Class
SR : Strontium ranelate
TEN : Toxic Epidemal Necrolysis
TME : Targeted Medical Events
ULN : Upper Limit of Normal range
USR : Urgent Safety Restriction

1. Steps taken for the assessment

This is the assessment of PSUR(s) received for strontium ranelate with a DLP 21 September 2012 as follows:

MAH	Marketing authorisations concerned	Submission date
Les Laboratoires Servier	Protelos	3 December 2012
Les Laboratoires Servier	Osseor	3 December 3012

The steps taken for the procedure were:

Start of procedure:	13 December 2012
PRAC Rapporteur's preliminary assessment report circulated on:	15 February 2013
MAH comments on the Rapporteur preliminary assessment report received on:	13 March 2013
PRAC Rapporteur's updated assessment report circulated on:	28 March 2013
An Oral explanation took place on:	8 April 2013
PRAC recommendation:	11 April 2013

2. PSUR Data

2.1. Introduction

Strontium ranelate, the active substance of Protelos/Osseor, comprises of two atoms of stable strontium and one molecule of ranelic acid. Strontium ranelate dissociates at the gastrointestinal level. Strontium is a cation chemically and physiologically closely related to calcium. Ranelic acid is an organic, highly polar molecule without pharmacological activity. It is suggested that strontium acts through dual mechanisms of inhibition of resorption by osteoclasts and maintenance or stimulation of bone formation by osteoblasts. Strontium ranelate (Protelos/Osseor) is currently indicated for treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures and the treatment of osteoporosis in men at increased risk of fractures.

This assessment report is based on the 13th PSUR covering the period from 22 September 2011 to 21 September 2012.

2.2. Worldwide marketing authorisation status

Strontium ranelate, 2 g granules for oral suspension has been approved in more than 100 countries. Strontium ranelate was first authorised in the European Union on 21 September 2004.

2.3. Overview of exposure and safety data

2.3.1. Actions taken in the reporting interval for safety reasons

Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 14 October 2011 the opinion of the CHMP on measures necessary to ensure the safe and effective use of the strontium ranelate-containing osteoporosis medicinal products Protelos and Osseor. In particular, the CHMP was asked to review the risks of venous thromboembolism (VTE) and severe skin hypersensitivity reactions and its impact on the benefit risk balance.

The procedure started on 20 October 2011.

The Committee concluded on 15 March 2012 that the benefit/risk balance of strontium ranelate is favourable under normal conditions of use, subjected to certain changes to the product information (see 2.3.2) and the agreed updated risk management plan.

A prescription survey was to be carried out in order to evaluate prescriber awareness concerning the content of the updated SmPC. Regarding the ongoing clinical trials with strontium ranelate, amendments to the protocol, patient information consent and updated investigator's brochure were implemented.

Further to the extension of indication for the treatment of osteoporosis in adult men at increased risk of fracture, the MAH was requested to undertake the two below studies as set out in the Pharmacovigilance plan of the RMP:

- To conduct a prospective observational cohort study to evaluate the incidence of fractures and the adherence and tolerability of strontium ranelate in osteoporotic men treated with strontium ranelate in the post-marketing setting.
- To perform a retrospective study in osteoporotic patients to further assess the risk of ischaemic cardiac events, using the CPRD database.

2.3.2. Changes to reference safety information

The Reference Safety Information (RSI) for this PSUR corresponds to the sections 4.3 to 4.9 of the SmPC of strontium ranelate approved in Europe at the end of the period covered by the PSUR and dated on 25 May 2012.

Further to the benefit/risk review under Article 20 of Regulation (EC) No 726/2004, the SmPC was updated as follows:

Addition of a new contraindication for patients with current or previous VTE including deep vein thrombosis and pulmonary embolism as well as in permanently or temporarily immobilized patients; Update of the precautions for use: the need for continued treatment should be re-evaluated in patients over 80 years at risk of VTE; the description of sign and symptoms of skin reactions were updated in agreement with key elements adopted by the PhVWP in September 2011 concerning SJS and TEN for 'high risk' drugs.

Further to the signal detection process, a type II variation (submitted in June 2012 to the CHMP) was approved on 23 October 2012. The section 4.8 of the SmPC has been updated to add "paraesthesia", "dry mouth", "vertigo", "dizziness" and "malaise" as undesirable effect .

The section 4.4 of the SmPC has also been updated to mention that a higher occurrence of severe skin hypersensitivity reactions such as SJS, TEN or skin rash was observed in patients of Asian origin.

2.3.3. Estimated exposure and use patterns

Cumulative subject exposure in clinical trials

Since the beginning of the development of strontium ranelate until 21 September 2012, 24 phase II-III clinical studies have been performed:

- 17 are completed of which 6 were completed during the period
- 7 are still on-going (including 1 frozen study).

Estimates of cumulative subject exposure by indication are provided in the table below

Table 1 - Cumulative number of subjects by indication

		S12911* (All)	Placebo	Alendronate	All
All indications	N (NPY)	**8017 (35867.7)**	**5036 (19944.5)**	**269 (340)**	**13322 (56152.2)**
Post-menopausal osteoporosis	N (NPY)	6267 (24010.2)	4168 (14314.9)	269 (340.0)	10704 (38665.1)
Male osteoporosis	N (NPY)	263 (559.3)	96(160.3)		359 (719.6)
Osteoarthritis	N (NPY)	1487 (11298.1)	772 (5469.3)		2259 (16767.5)

Number of patients(N) and number of Patient-Years (PY)
Exposure = (Time between first intake and last contact date or cut-off date for patients on going) +1 day
S12911* corresponds to all patients treated either by S12911 or by S06911 at any dose
S12911= Strontium Ranelate S06911= Fixed combination Strontium Ranelate and vitamin D

2.3.4. Data in summary tabulations

Table 2. Cumulative summary tabulations of serious adverse events from clinical trials: (SOC cardiac disorders, SOC injury, poisoning and procedural complications (includes fractures)

In postmenopausal osteoporosis

12911 corresponds to all patients treated either by 12911 or by 06911*

PRIMARY SOC / PREFERRED TERM	12911 0.125g (N=40)		12911 0.5g (N=125)		12911 1g (N=130)		12911 2g (N=5934)		12911* All (N=6229)		Placebo (N=4152)	
	n(1)	%(2)	n(1)	%(2)	n(1)	%(2)	n (1)	%(2)	n(1)	%(2)	n(1)	%(2)
ALL	4	10.00	19	15.20	19	14.62	1858	31.31	1900	30.50	1211	29.17
Cardiac disorders	0	0.00	1	0.80	1	0.77	473	7.97	475	7.63	273	6.58
Atrial fibrillation	0	0.00	0	0.00	0	0.00	87	1.47	87	1.40	51	1.23
Cardiac failure	0	0.00	0	0.00	0	0.00	75	1.26	75	1.20	47	1.13
Angina pectoris	0	0.00	0	0.00	0	0.00	68	1.15	68	1.09	50	1.20
Myocardial infarction	0	0.00	0	0.00	1	0.77	57	0.96	58	0.93	26	0.63
Acute myocardial infarction	0	0.00	0	0.00	0	0.00	43	0.72	43	0.69	14	0.34
Myocardial ischaemia	0	0.00	0	0.00	0	0.00	25	0.42	25	0.40	15	0.36
Coronary artery disease	0	0.00	0	0.00	0	0.00	26	0.44	26	0.42	8	0.19
Angina unstable	0	0.00	0	0.00	0	0.00	18	0.30	18	0.29	10	0.24

Sick sinus syndrome	0	0.00	0	0.00	0	0.00	17	0.29	17	0.27	7	0.17
Arrhythmia	0	0.00	0	0.00	0	0.00	16	0.27	16	0.26	8	0.19
Cardiac failure congestive	0	0.00	0	0.00	0	0.00	17	0.29	17	0.27	2	0.05
Cardiac arrest	0	0.00	0	0.00	0	0.00	8	0.13	8	0.13	9	0.22
Left ventricular failure	0	0.00	0	0.00	0	0.00	10	0.17	10	0.16	5	0.12
Cardiac failure chronic	0	0.00	0	0.00	0	0.00	11	0.19	11	0.18	2	0.05
Bradycardia	0	0.00	0	0.00	0	0.00	7	0.12	7	0.11	6	0.14
Atrioventricular block complete	0	0.00	0	0.00	0	0.00	8	0.13	8	0.13	2	0.05
Supraventricular tachycardia	0	0.00	0	0.00	0	0.00	7	0.12	7	0.11	3	0.07
Atrial flutter	0	0.00	0	0.00	0	0.00	6	0.10	6	0.10	3	0.07
Arteriosclerosis coronary artery	0	0.00	0	0.00	0	0.00	5	0.08	5	0.08	4	0.10
Atrioventricular block second degree	0	0.00	0	0.00	0	0.00	5	0.08	5	0.08	3	0.07
Aortic valve stenosis	0	0.00	0	0.00	0	0.00	4	0.07	4	0.06	4	0.10
Cardiopulmonary failure	0	0.00	0	0.00	0	0.00	4	0.07	4	0.06	4	0.10
Atrioventricular block	0	0.00	0	0.00	0	0.00	5	0.08	5	0.08	1	0.02
Mitral valve incompetence	0	0.00	0	0.00	0	0.00	3	0.05	3	0.05	5	0.12
Tachyarrhythmia	0	0.00	0	0.00	0	0.00	3	0.05	3	0.05	3	0.07
Cardiovascular disorder	0	0.00	0	0.00	0	0.00	3	0.05	3	0.05	0	0.00
Nodal arrhythmia	0	0.00	0	0.00	0	0.00	3	0.05	3	0.05	0	0.00
Right ventricular failure	0	0.00	1	0.80	0	0.00	2	0.03	3	0.05	0	0.00
Ischaemic cardiomyopathy	0	0.00	0	0.00	0	0.00	3	0.05	3	0.05	0	0.00
Supraventricular extrasystoles	0	0.00	0	0.00	0	0.00	2	0.03	2	0.03	1	0.02
Atrial tachycardia	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	2	0.05
Atrioventricular block first degree	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	2	0.05
Bundle branch block right	0	0.00	0	0.00	0	0.00	2	0.03	2	0.03	0	0.00
Cardio-respiratory arrest	0	0.00	0	0.00	0	0.00	2	0.03	2	0.03	0	0.00
Coronary artery occlusion	0	0.00	0	0.00	0	0.00	2	0.03	2	0.03	0	0.00
Hypertensive heart disease	0	0.00	0	0.00	0	0.00	2	0.03	2	0.03	0	0.00
Palpitations	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	2	0.05
Pericarditis	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	2	0.05
Sinoatrial block	0	0.00	0	0.00	0	0.00	2	0.03	2	0.03	0	0.00
Sinus bradycardia	0	0.00	0	0.00	0	0.00	2	0.03	2	0.03	0	0.00
Tachycardia	0	0.00	0	0.00	0	0.00	2	0.03	2	0.03	0	0.00
Ventricle rupture	0	0.00	0	0.00	0	0.00	2	0.03	2	0.03	0	0.00
Ventricular tachycardia	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	2	0.05
Coronary artery insufficiency	0	0.00	0	0.00	0	0.00	2	0.03	2	0.03	0	0.00
Cardiac valve disease	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	2	0.05
Mitral valve disease	0	0.00	0	0.00	0	0.00	2	0.03	2	0.03	0	0.00
Aortic valve disease	0	0.00	0	0.00	0	0.00	2	0.03	2	0.03	0	0.00
Heart valve incompetence	0	0.00	0	0.00	0	0.00	2	0.03	2	0.03	0	0.00
Arteriospasm coronary	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	1	0.02
Ventricular extrasystoles	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	1	0.02
Ventricular fibrillation	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	1	0.02
Ventricular failure	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	1	0.02
Arrhythmia supraventricular	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	0	0.00
Bundle branch block left	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	0	0.00
Cor pulmonale chronic	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	0	0.00
Coronary artery stenosis	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	0	0.00
Mitral valve prolapse	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	0	0.00
Myocardial rupture	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	0	0.00
Pericardial effusion	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	0	0.00
Sinus tachycardia	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	0	0.00
Ventricular arrhythmia	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	0	0.00
Wolff-Parkinson-White syndrome	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	0	0.00
Bradyarrhythmia	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2	0.05
Non-obstructive cardiomyopathy	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	0	0.00
Paroxysmal arrhythmia	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	0	0.00
Acute coronary syndrome	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	0	0.00
Pleuropericarditis	0	0.00	0	0.00	0	0.00	1	0.02	1	0.02	0	0.00
Adams-Stokes syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.02
Cardiac amyloidosis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.02
Cardiac hypertrophy	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.02
Cardiac tamponade	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.02
Coronary artery thrombosis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.02
Extrasystoles	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.02
Myocardial fibrosis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.02
Restrictive cardiomyopathy	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.02
Congestive cardiomyopathy	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.02
Cardiac disorder	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.02

Injury, poisoning and procedural complications	0	0.00	4	3.20	6	4.62	151	2.54	161	2.58	109	2.63

In male osteoporosis

12911 corresponds to all patients treated either by 12911 or by 06911*

PRIMARY SOC / PREFERRED TERM	12911* 2g (N=235)		12911* All (N=235)		Placebo (N=96)	
	n (1)	% (2)	n (1)	% (2)	n (1)	% (2)
ALL	58	24.68	58	24.68	27	28.13
Cardiac disorders	13	5.53	13	5.53	4	4.17
Coronary artery disease	4	1.70	4	1.70	0	0.00
Acute myocardial infarction	3	1.28	3	1.28	1	1.04
Angina pectoris	2	0.85	2	0.85	0	0.00
Coronary artery stenosis	1	0.43	1	0.43	2	2.08
Atrial fibrillation	1	0.43	1	0.43	0	0.00
Bradycardia	1	0.43	1	0.43	0	0.00
Cardiac failure chronic	1	0.43	1	0.43	0	0.00
Cardiac failure congestive	1	0.43	1	0.43	0	0.00
Mitral valve prolapse	1	0.43	1	0.43	0	0.00
Myocardial infarction	1	0.43	1	0.43	0	0.00
Myocardial ischaemia	1	0.43	1	0.43	0	0.00
Ventricular extrasystoles	1	0.43	1	0.43	0	0.00
Left ventricular failure	0	0.00	0	0.00	1	1.04
Injury, poisoning and procedural complications	7	2.98	7	2.98	3	3.13

In osteoarthritis

12911 corresponds to all patients treated either by 12911 or by 06911*

PRIMARY SOC / PREFERRED TERM	12911 1g (N=548)		12911* 2g (N=586)		12911* All (N=1134)		Placebo (N=577)	
	n (1)	% (2)	n (1)	% (2)	n (1)	% (2)	n (1)	% (2)
ALL	99	18.07	105	17.92	204	17.99	105	18.20
Cardiac disorders	11	2.01	19	3.24	30	2.65	7	1.21
Atrial fibrillation	5	0.91	4	0.68	9	0.79	3	0.52
Angina pectoris	1	0.18	3	0.51	4	0.35	0	0.00
Acute myocardial infarction	1	0.18	2	0.34	3	0.26	0	0.00
Coronary artery disease	1	0.18	2	0.34	3	0.26	0	0.00
Myocardial infarction	1	0.18	2	0.34	3	0.26	0	0.00
Angina unstable	0	0.00	2	0.34	2	0.18	0	0.00
Acute coronary syndrome	0	0.00	2	0.34	2	0.18	0	0.00
Supraventricular tachycardia	0	0.00	1	0.17	1	0.09	1	0.17
Atrial flutter	0	0.00	1	0.17	1	0.09	0	0.00
Atrioventricular block complete	1	0.18	0	0.00	1	0.09	0	0.00
Bradycardia	1	0.18	0	0.00	1	0.09	0	0.00
Cardiac failure	0	0.00	1	0.17	1	0.09	0	0.00
Cardiac tamponade	1	0.18	0	0.00	1	0.09	0	0.00
Coronary artery stenosis	1	0.18	0	0.00	1	0.09	0	0.00
Mitral valve incompetence	0	0.00	1	0.17	1	0.09	0	0.00
Nodal rhythm	0	0.00	1	0.17	1	0.09	0	0.00
Sick sinus syndrome	1	0.18	0	0.00	1	0.09	0	0.00
Sinus tachycardia	0	0.00	1	0.17	1	0.09	0	0.00
Coronary artery thrombosis	0	0.00	0	0.00	0	0.00	1	0.17
Myocardial ischaemia	0	0.00	0	0.00	0	0.00	1	0.17
Ventricular tachycardia	0	0.00	0	0.00	0	0.00	1	0.17

Since the beginning of the development of strontium ranelate, a total of 2,162 patients reported in clinical trials at least one serious adverse event under strontium ranelate and 1,343 under placebo. The

proportion of patients with serious adverse events was similar in strontium ranelate and placebo groups. For cardiovascular disorders SOC:

Cardiovascular disorders	**SrRan 2g**	**Placebo**
Post-menopausal osteoporosis	7.97%	6.58%
Male osteoporosis	5.53%	4.17%
Osteoarthritis	3.24%	1.21%

The presented data shows a numerically larger proportion of patients with cardiac disorders in the strontium ranelate 2g group compared to placebo in all study populations; this seems to be the case especially for ischemic cardiac events. However, numbers for different types of cardiovascular disease are difficult to interpret from the data submitted by the MAH.

In general, cardiac disorders SOC were more frequent in osteoporotic populations compared to reported serious adverse events in the SOC "injury, poisoning and procedural complications" that includes fractures. This might be considered in the benefit-risk assessment of strontium ranelate as the actual indication is reduction of vertebral and hip fractures. Increases in the relative risk of cardiac disorders (21% in women and 33% in men) might have a greater clinical relevance in osteoporosis population than similar relative risk reductions in fractures. However, as fractures were efficacy endpoints in the majority of these studies, all these events may not have been reported as serious adverse events. These numbers should be compared with pooled efficacy data.

In addition, "nervous system disorders" that includes cerebrovascular disease was more common in strontium ranelate 2g compared to placebo (6.17% vs 4.91%). The different types of nervous system disorders are difficult to interpret from the data submitted by the MAH.

For all of these events, it is acknowledged that patients in the strontium and control groups may have been treated for different amount of time. Thus, there is a need for additional data presentation where the time aspect is taken into account. Further, it is also of importance to evaluate when the events occur in relation to treatment start.

Table 3. Cumulative and interval summary tabulations of serious and non-serious adverse reactions (Sub total CSR) from post-marketing data sources

ADR Term	**Spontaneous, including competent authorities (worldwide) and literature**				**Total Spontan**	**Non-interventional post-marketing study and reports from other solicited sources**	
	Serious		**Non-Serious**			**Serious**	
	Intervall	**Cumul**	**Intervall**	**Cumul**	**Cumul All**	**Intervall**	**Cum ul**

Blood and lymphatic system disorders	28	103	11	110	209	0	3
Cardiac disorders	41	106	11	82	182	1	8
Congenital disorders	0	1	0	0	1	0	0
Ear and labyrinth disorders	7	26	12	76	102	0	0
Endocrine disorders	2	5	0	10	15	0	0
Eye disorders	16	63	13	147	207	1	6
Gastrointestinal disorders	66	287	364	2196	2446	4	34
General disorders	66	226	121	774	980	3	19
Hepatobiliary disorders	10	53	5	23	74	0	0
Immune system disorders	1	16	8	29	45	0	2
Infections and infestations	24	80	26	170	246	1	10
Injury, poisoning and procedural complications	24	57	12	56	107	0	10
Investigations	60	166	66	565	709	1	6
Metabolism and nutrition disorders	20	57	13	119	175	0	2
Musculoskeletal and connective tissue disorders	44	149	127	812	954	1	10
Neoplasms	10	32	2	14	46	1	4
Nervous system disorders	56	291	118	878	1146	4	33
Psychiatric disorders	17	64	38	263	320	0	7
Renal and urinary disorders	16	61	14	116	171	1	6
Reproductive system and breast disorders	1	7	5	47	54	0	1
Respiratory, thoracic and mediastinal disorders	92	314	30	289	588	4	36

Skin and subcutaneous tissue disorders	99	476	230	1627	2055	8	50
Social circumstances	3	5	0	0	5	0	0
Surgical and medical procedures	1	9	1	3	11	2	3
Vascular disorders	78	357	26	153	501	3	54

The PRAC noted that no comparisons between the previous PSUR periods have been presented by the MAH in this PSUR.

According to data from the previous PSUR (covering the period from 22 September 2010 to 21 September 2011), the overall reporting rate was similar in this PSUR period (1,092 cases) compared to the previous period (1,266 cases). The distribution of all reported adverse reactions between SOC was about similar to the previous PSUR period. However, the number of serious cardiac disorders cases has increased from 26 during previous PSUR to 41 during this PSUR period.

2.3.5. Summaries of significant findings from clinical trials in the reporting interval

During the period covered by this report, 6 new clinical studies were analysed (study report available) and presented: studies CL3-12911-018, CL3-12911-025, CL3-12911-030, CL3-12911-032 (2 years), CL3-06911-002, CL3-06911-003.

In the CL3-12911-032 study in male osteoporotic patients (173 strontium ranelate treated patients and 87 placebo-treated patients), over the 2 years of treatment, the overall incidence of emergent adverse events was lower in the strontium ranelate group as compared to placebo, with a similar incidence of emergent serious adverse events. A higher incidence in cardiac events between treatment groups was observed (16.2% versus 13.8%, respectively in the strontium ranelate versus the placebo group), the difference being mainly due to angina pectoris (4.0% versus none, respectively) and coronary artery disease (2.5% versus 1.1%, respectively). This should be interpreted in the light of a similar imbalance in the relevant medical histories in the study population with a higher percentage of patients in the Strontium ranelate group as compared to the placebo group with a medical history of ischaemic coronary artery disease (16.2% versus 11.5%, respectively), in particular, myocardial ischaemia (10.4% versus 3.4%, respectively), glucose metabolism disorders (11.0% versus 6.9%) and hypertension (42.8% versus 39.1%). Considering cardiac AE in both CL3-12911-032 and PMO studies, the relative risk of ischaemic heart disease in the strontium ranelate group compared to placebo was not significantly increased in neither of the phase III trials, with an adjusted hazard ratio of 1.24 [0.49 ; 3.17] in the CL3-032 study, 1.13 [0.95 ; 1.34] and 0.83 [0.58 ; 1.18] in the TROPOS and SOTI studies, respectively.

Based on these findings it was proposed to provide the EMA with the results of a specific study based on the CPRD database in UK which includes a large number of osteoporotic patients treated with Strontium ranelate. The primary results of this nested case-control study indicate no proof of evidence of a higher risk of myocardial infarction or cardiovascular death associated with the use of Strontium ranelate in women treated for osteoporosis in current medical practice.

In the CL3-12911-018 study in men and women with osteoarthritis, (558 SR 1 g treated patients, 566 SR 2 g treated patients and 559 placebo treated patients) the incidence of emergent adverse events and of serious emergent adverse events was similar in the 3 groups. The overall incidence of cardiac disorders was similar in the 3 groups (5.5%, 5.7% and 5.8% respectively). However, the number of cardiac disorders classified as severe, serious, leading to study drug withdrawal and considered as treatment related were higher in the Strontium ranelate groups. This will be further documented by the MAH and answers will be provided to EMA by 21 December 2012.

In the CL3-12911-025 study conducted in 387 postmenopausal women with osteoporosis (255 treated with Strontium ranelate, 132 with alendronate), the overall clinical and bone safety did not show any unexpected event. In particular no sign of osteomalacia, and mean bone Strontium contents after 6 months and one year of treatment consistent with those observed in previous studies and below those for which bone deleterious effects occurred in animals. Bone lymphoid nodes were reported in 20 patients (9.7%) in the Strontium ranelate group *versus* 1 patient (0.9%) in the alendronate group. Although more frequent than in the alendronate group, this incidence remains within known ranges especially in the elderly (lymphoid nodes reported in up to 4% of patients without lymphoproliferative disorders). Those lymphoid nodes were mostly isolated and of normal type and size. No relevant finding in favour of blood cytopenic disorder or bone marrow failure or lymphoproliferative disorder or auto immune disease was evidenced in any of the 21 patients with lymphoid nodes on their post-baseline biopsy. Complementary information is currently under evaluation by the EMA. In addition, this event is currently under assessment by the MAH and is considered as an on-going signal.

In CL3-12911-030 study**:** this study was designed to assess the effects of a two-year administration of 2g per day of Strontium ranelate versus alendronate 70mg per week in women with postmenopausal osteoporosis on bone geometry and bone strength measured by peripheral-Quantitative Computed Tomography (p-QCT). An overrepresentation of eye disorders and cataract was reported in Strontium ranelate treated patients (15.4% of patients in the SR group *versus* 3.2% in the alendronate group) but possibly explained by differences already present at baseline (9 patients: 9.9% in SR group *versus* 2 patients: 2.1% in the alendronate group). The complementary analysis of all the cases of eye disorders and cataract did not show an increased incidence of eye disorders or cataract in placebo-controlled clinical trial (OSA 2011 in post-menopausal osteoporotic women) as well as in the 3-year post- marketing trial in 12076 patients and no signal was reported from the post-marketing surveillance.

S06911 is a fixed combination of Strontium ranelate and vitamin D. During the reporting period, 2 clinical studies were completed (**CL3-06911-002 and CL3-06911-003**). A higher incidence of hypercalciuria as adverse event was observed in patients treated with Strontium ranelate/ cholecalciferol compared to Strontium ranelate alone which is expected according to the mechanism of action of vitamin D. All cases were asymptomatic and none was associated with other potential signs of vitamin D toxicity.

2.3.6. Findings from non-interventional studies

During the period of this PSUR, 3 non interventional studies were completed with strontium ranelate.

Study CLE-12911-021 is a European observational, non-interventional survey, which was set up to evaluate the profile of post-menopausal osteoporotic women in current medical practice and to assess safety of use of Strontium ranelate treatment and in particular the frequency of VTEs in patients follow-up over 3 years. The safety set consisted of 12 076 patients for which data were available after

the inclusion visit with a mean follow-up time of 32.0 ± 9.7 months, and an exposure of 24 956 patient-years (PY). The study report was submitted as a follow-up measure on 16 November 2011 and considered as fulfilled by EMA on 25 April 2012.

Study GPRD-VTE: A study was performed on data from the General Practice Research Database (GPRD). The main objective of this study was to evaluate and quantify the risk of VTE in untreated osteoporotic women (n=15846) and in osteoporotic women newly treated with Strontium ranelate (n = 6454) or alendronate (n = 59173) in current practice. The study report was submitted as a follow-up measure on 16 November 2011 and considered as fulfilled by EMA on 25 April 2012.

Study DSRU is an independent Prescription-Event Monitoring study analysis conducted by the Drug Safety Research Unit (DSRU) in UK. The study was designed to examine the safety and use of Strontium ranelate prescribed in general practice in England. An additional question requested specific information on history of VTE. The final cohort consisted of 10,865 patients who were prescribed strontium ranelate, using PEM methodology. Overall, strontium ranelate was considered to be reasonably well tolerated in the immediate post-marketing period.

2.3.7. Information from other clinical trials and sources

In order to assess more accurately the cardiovascular safety in both men and post-menopausal women, a specific study in osteoporotic patients to further assess the risk of ischaemic cardiac events, using the UK Clinical Practice Research Datalink (CPRD) database was set up during the period covered by this report. The analyses are still on-going and the final study report will be submitted when available.

Primary results: The case-control analysis on cardiovascular death was nested in a cohort of 64,831 patients eligible to ONS linkage. Among 3 619 cardiovascular death cases identified in mortality data, 3,516 were matched to 34,982 controls.

Table 4 - Association of Strontium ranelate / Alendronate with ischemic cardiac events in CPRD – Primary analyses

	First definite MI Cases=1336 / Controls=13330 Adjusted OR [95% CI] (*)	**MI with hospitalisation** Cases=1433 / Controls=14,261 Adjusted OR [95% CI] (*)	**Cardiovascular death** Cases=3516 / Controls=34,982 Adjusted OR [95% CI] (*)
Current use			
Alendronate	1 (reference)	1 (reference)	1 (reference)
SR	1.13 [0.74;1.73]	1.12 [0.72;1.74]	1.27 [1.00;1.61]

The MAH stated that the primary results of this nested case-control study did not evidence a higher risk of myocardial infarction or cardiovascular death associated with the use of Strontium ranelate in women.

However, the PRAC questioned the MAH's statement as the risk of cardiovascular death was increased in strontium ranelate treated women compared to alendronate treated, OR 1.27, the numbers indicate borderline significance. However, the final results will be submitted when available.

2.3.8. Other periodic reports

The MAH responded to questions raised during the assessment of the previous PSUR.

1. Comment on the outcome and actions of the ongoing article 20 procedure

The European Medicines Agency (EMA) confirmed the favourable benefit-risk balance of Strontium ranelate on 15 March 2012. The SmPC and PL were updated as follows. In order to reduce the risk of VTE, the existing precautions for use were strengthened. Use of Strontium ranelate is now contraindicated in patients with current or previous VTE, as well as in permanently or temporarily immobilized patients. Doctors should reevaluate the need to continue treatment with Strontium ranelate in patients over 80 years at risk of VTE. In order to improve the management of patients experiencing skin hypersensitivity, the description of signs and symptoms was updated in the Summary of Product Characteristics.

In order to measure the effectiveness of the SmPC changes, a prescription survey will be carried out in order to evaluate prescriber awareness concerning the content of the SmPC with particular emphasis on the introduction of a new contraindication (current or previous VTE), including deep vein thrombosis or pulmonary embolism; Temporary or permanent immobilisation due to (e. post-surgical recovery or prolonged bed rest). The study results will be available by Q2 2013.

The PRAC considered this issue resolved. Results from the prescription study are to be presented in the next PSUR.

2. The MAH is requested to submit detailed analyses and comments on the three (S11006038, S11003543, S11005985) reported cases of Interstitial nephritis with acute renal failure.

In the PSUR 12, the cases of Acute renal failure (ARF) occurred in a context of Tubulo-interstitial nephritis were not analysed separately because considered as a part of Tubulo-interstitial nephritis which were already analysed.

Short narratives for these three cases are presented. The acute renal failure was secondary to an acute interstitial nephritis in a context of severe hypersensitivity reaction assessed by the Expert Committee as possible DRESS in one case, concomitant treatments with NSAID and omeprazole were present in another case. The role Protelos in the occurrence of Interstitial nephritis and consequently of ARF cannot be ruled out in these 2 cases but seemed to be unlikely in remaining 1 case. No new safety concern was identified regarding acute renal failure.

The PRAC considers that the signal of interstitial nephritis should remain as a potential risk in the RMP (see signal evaluation).

3. The MAH should continue to monitor cases of off-label use.

	Number of cases	
	Cumulative number since 21 Sep 2004	PSUR Period (22 Sep 2011 to 21 Sep 2012)
Pregnant and lactating women	3*	0
Children < 18 year-old	9	4
Pre-menopausal women	112	18
Male over 18 year-old	337	96
Total	**458**	**118**

**3 cases also counted in "pre-menopausal women"*

The adverse events observed and reported in specific populations were similar to those reported in the target population.

The PRAC considered this issue to be resolved.

4. In the Overall Summary table (9.6).1 Section 6, the specification of serious unlisted and non-serious unlisted seems to be omitted for PSUR 10, 11 and 12. The data extracted from Appendix 6 suggests that approximately 1.5 more unlisted serious events were reported per patient-month for this PSUR period compared to the previous (917 vs 283). The MAH should comment.

In November 2010, the MAH implemented new seriousness upgrade conventions according to predefined internal rules through a systematic review of all cases containing events from the MedDRA Important Medical Events (IME). These rules were implemented at the beginning of the PSUR 12 period. This accounts for the increase of the serious events number during the PSUR 12 period compared to the PSUR 11 period.

(see PRAC conclusions on question 5)

5. The MAH is requested to submit a similar summary table as the one presented in PSUR 11(Table (9)1) in the next upcoming PSUR (PSUR 13) listing all the above different events in relation to the previous PSUR period (PSUR 12).

The MAH provided the following table:

	PSUR 10 (6 months)			**PSUR 11 (6 months)**			**PSUR 12 (12 months)**		
	HCP	N-HCP	Total	HCP	N-HCP	Total	HCP	N-HCP	Total
Number of patient-cases (serious)	296(98)	180(2)	476(100)	336(126)	187(11)	523 (137)	836 (351)	480 (57)	1316 (408)
Number of unlisted adverse events	674	355	1 025	840	392	1232	2084	1068	3152
Serious (unlisted)	272(132)	6(4)	278(136)	439(269)	22(14)	461(283)	1266(776)	212(141)	1478(917)
Non serious (unlisted)	402(188)	349(183)	751(371)	401(231)	370(226)	771(457)	718(366)	856(473)	1674(839)

A similar table is not presented in the PSUR 13 in accordance with the new PSUR format and content (GVP Module VII). All the unlisted events, serious and not serious, are closely monitored through the internal signal detection process.

As stated by the MAH, the new PSUR format does not include this form of a table. However, an increase in serious unlisted events in PSUR 12 should be followed up, and a table including PSUR 13 period would be informative. The MAH was requested to present a similar summary table including also PSUR 13 period.

6. The detailed narratives of the photosensitivity cases are difficult to find in the line listings. Please present these within the safety overview of the next PSUR.

The narratives of the 5 cases of photosensitivity reported during the period of the PSUR 12 are presented below. Further to internal signal detection procedure, photosensitivity was considered as a false signal during the PSUR 13 period.

From the presented case narratives, the link between treatment and photosensitivity reaction is considered possible in 4/5 cases. The signal is discussed in chapter 3 in this PSUR 13.

7. A follow-up of the reporting frequency of the unlisted events Dizziness and Fatigue should be presented.

A cumulative review of "dizziness" and "fatigue" is presented in chapter 3 in this PSUR 13.

Dizziness: The overall estimated incidence of "dizziness" remains stable overtime: 5.0/100 000 PY up to 21 September 2011 (PSUR 12) versus 5.3/100 000 PY up to 21 September 2012 (PSUR 13). However, further to the internal signal detection process this event was categorized as non-important identified risk and the section 4.8 of the SmPC was updated (type 2 variation approved by European commission on 23 October 2012).

The PRAC considered this issue resolved.

8. Clarification on whether the 4 cases of pulmonary embolism and 3 cases of DRESS addressed in Section 7 have been included in the compiled analysis of cases of venous thromboembolism (VTE) and drug rash with eosinophilia and systemic symptoms (DRESS) submitted within the ongoing article 20 procedure.

The 4 cases of pulmonary embolism and 3 cases of DRESS were received after the data lock point of the PSUR 12 and consequently were not included in the compiled analysis submitted within the article 20 procedure. These cases were included in the characterization of the risks presented in this PSUR 13.

The PRAC considered this issue resolved.

9. The MAH should further comment on the diagnosis and coding of the fatal case with asthma.

This elderly patient with a medical history of asthma and several co-morbiditie factors such as hypertension, general frailty, transient ischemic attacks died following an asthmatic crisis leading to respiratory distress. A respiratory hypersensitivity/allergic reaction cannot be ruled out. Bronchial hyperreactivity including wheezing and dyspnea is a known side effect of Protelos (part 4.8 of RCP).

MHRA coded the events (MedDRA version 13.1) as follows: LLT Death unexplained (PT Death unexplained), LLT Respiratory Distress (PT Respiratory distress), LLT Laboured breathing (PT Dyspnoea) and LLT Wheezing (PT Wheezing).

MAH has respected all codes reported by MHRA and considered the coding of all reported events as correct

The PRAC considered this issue resolved.

10. The MAH is requested to submit narratives for the five cases of male gynaecomastia.

The narratives of the 5 cases of gynaecomastia reported during the period of the PSUR 12 were presented by the MAH.

According to the narratives, the link between treatment and gynecomastia is considered possible in 3/5 cases. None of the cases is considered serious. Issue not further pursued.

11. The requested clarification in the previous PSUR (PSUR 11) why there is a discrepancy in total number of serious unlisted and non-serious unlisted adverse events shown in table (9)2 and table 9(3) is missing and should be addressed in the next PSUR.

At that time, the listedness criteria of the events was compiled in both tables manually and the discrepancy was due to a human error. The correct number of serious and non serious unlisted events should refer to the table (9)1. Of note, all serious unlisted events were correctly analyzed in the section 6.3 Serious unlisted cases.

Corrective actions on the PSUR writing process were undertaken. All requests used for table generation have been validated and are automatized. Furthermore, quality control on cumulative data is now performed.

The PRAC considered this issue resolved.

2.4. Discussion and conclusions on PSUR data

The MAH has presented a one-year PSUR for strontium ranelate. The total numbers of serious unlisted events recorded for the period are not clear from the MAH presentation according to the new PSUR template. The MAH has not presented analyses of the report rate through all PSUR periods. An increase in serious unlisted events in the previous PSUR 12 should be followed up and the MAH is requested to present a summary table including PSUR 13 period.

Clinical trials during the reporting interval have raised the following new safety concerns: cardiovascular safety, bone marrow anomalies (lymphoid nodes) and eye disorders. These signals are discussed in chapter 3. Hypercalciuria was identified in the study with fixed combination of strontium ranelate and vitamin D study which was expected according to the mechanism of action of vitamin D.

The MAH has updated the RMP regarding the important potential risk of myocardial infarction in osteoporotic post-menopausal women based on clinical trials. Ischemic heart disease in osteoporotic men has been added as important missing information. As discussed above, and also further below under signal evaluation, there is a need for further data presentation and evaluation of cardiovascular safety and its impact on the benefit/risk balance.

Several previous risks were reassessed according to the definition provided in GVP Annex I definitions and considered now as false signals or non-important identified risks. All of these aspects are further discussed below.

A cumulative review of all safety issues that are defined in the RMP is presented in chapter 3.

3. Signal and risk evaluation

Summary of safety concerns

During the interval period:

- 3 new validated signals were identified (still on-going at the data lock point):

In Asian population: Stevens-Johnson Syndrome (SJS) and Toxic Epidemal Necrolysis (TEN),

Ischaemic heart diseases in osteoporotic men, and

Bone lymphoid nodes.

- 15 validated signals were closed during the interval period.
- No signal was on-going at the beginning of the period covered by this report.

The table below summarizes all identified and potential risks and missing or limited information as of the beginning of the reporting interval of the current PSUR.

Table 5. Summary of important safety concerns at the beginning of the PSUR period (Current approved RMP)

Identified risks	- VTE - Hypersensitivity reactions -Hepatobiliary disorders: hepatitis and serum transaminase increased - Blood cytopenic disorders: bone marrow failure -Nervous System disorders: Seizures, disturbances in consciousness, memory loss, - Creatine Kinase increase and musculoskeletal disorders, - Psychiatric disorders: confusion and insomnia
Potential risks	- Interstitial nephritis - Psychiatric disorders: depression hallucination - Photosensitivity - Pancreatitis - Bone sarcoma - Hypertension - Skeletal accumulation of Strontium
Missing or limited information	- Children and adolescents (< 18 years old) - Pregnant and lactating women

Table 6. Important safety concerns in the proposed RMP

Summary of safety concerns related to active substance	
Important identified risks	- VTE - Hypersensitivity reactions - Nervous System disorders: Seizures, disturbances in consciousness - Hepatobiliary disorders: hepatitis and serum transaminase increased - Blood cytopenic disorders: bone marrow failure

Important potential risks	- Skeletal accumulation of strontium - Myocardial infarction in osteoporotic post-menopausal women
Important missing information	- Children and adolescents (< 18 years old) - Pregnant and lactating women - Ischemic heart disease in osteoporotic men - Long term safety in men with osteoporosis

The Strontium ranelate safety was assessed in the "OSA 2011 women osteoporosis" called OSA 2011 in this document, in the patients over 80 years old of the OSA 2011 and in the Long Term 2 g.

- The OSA 2011 was performed on the data from randomized Strontium ranelate studies in postmenopausal osteoporotic patients. This overall set consists of 3 805 Strontium ranelate-treated patients and 3 769 placebo-treated patients.

- The OSA 2011 in patients aged > 80 years consists of 761 Strontium ranelate-treated patients and 780 placebo-treated patients.

- The Long Term 2 g consists in post-menopausal osteoporotic patients treated at least once with Strontium ranelate 2 g or Strontium ranelate 2 g/vitamin D3 (1000 IU fixed combination) and includes 2 long-term open "extension study" It allows to assess the Strontium ranelate safety with an exposure up to 10 years. This set consists of 5 319 patients.

Signal evaluation

Cardiovascular safety signals

See also section summary tabulations 2.3.4, table 2 in this AR.

Closed signal that is now categorized as important potential risk:

Myocardial infarction in post-menopausal women

New signal categorized as important missing information

Ischemic heart disease in osteoporotic men

In the study on osteoporotic men, the incidence of cardiac disorders was higher in the Strontium ranelate group than in the placebo group over 2 years, mainly due to coronary artery disease (HLGT): angina pectoris, myocardial infarction (acute or not) and myocardial ischemia. Following these results, an analysis of cardiac adverse events in the post-menopausal osteoporosis studies (PMO) was performed. In the PMO studies (OSA 2011), a significant increase in myocardial infarctions was observed in Strontium ranelate group as compared to placebo group.

- **Post-menopausal osteoporotic patients**

The incidences of EAE "Myocardial infarction" (SMQ MI narrow, see Appendix 12) in OSA 2011 and in Long Term 2 g are presented in the table below:

	OSA 2011		Long term 2 g
	S12911 2g	Placebo	
N	3803	3769	5819
PT	11269.6	11250.1	19765.5
n(%)	64 (1.7)	40 (1.1)	97 (1.7)
PY	5.7	3.6	4.9
OR [95% CI]	1.60 [1.07;2.38]		
p-value	0.020		

N: Number of patients, PT: Number of patient-years by group
*n: Number of patients with at least one emergent AE Myocardial infarction, %: (n/N)*100*
PY: Number of patients with at least one emergent AE Myocardial infarction per 1000 patient-years
Estimate of the overall treatment effect (Mantel-Haenszel estimate): OR: odds ratio and CI: Confidence Interval.
p-value associated to the overall treatment effect

In OSA 2011 in patients with age≥80 years, similar number of patients presented with an EAE Myocardial infarction in the Strontium ranelate group as compared to the placebo group: 14 patients (1.8 %) out of 761 in the Strontium ranelate group *versus* 13 patients (1.7%) out of 780 in the placebo group.

Most of the affected patients had at least one cardiac risk factor. In clinical studies, the main risk factors were not specifically taken into account in the study population randomisation and the cardiac events have not been adjudicated by a dedicated committee.

Of note, in the post-menauposal osteoporotic women clinical studies, the risk of IHD in the Strontium ranelate group versus placebo was not statistically significantly increased with a HR [95%CI] of 1.10 [0.94; 1.28].

2) <u>In post-authorisation study cohort study</u>, among the 12 076 patients:

* 33 cases of myocardial infarction, acute coronary syndrome, acute myocardial infarction or coronary artery occlusion have been reported.

Among them, no events were considered as related to treatment by the investigator.

3) <u>In post-marketing surveillance</u>

Over the 96-months period of post-marketing surveillance, a total of 21 cases were reported. The estimated incidence is 0.6/100 000 PY and remains very low.

In 6 cases the diagnosis of myocardial infarction was excluded (5 events troponin increased reported in a context of confirmed pulmonary embolism and 1 acute MI was not confirmed by the autopsy which revealed a pulmonary embolism). The remaining 15 cases of "myocardial infarction" represent an estimated incidence of 0.5/100 000 PY.

Ischemic heart disease in male osteoporotic patients:

1) In male osteoporotic patients (study CL3-12911- 032)

	Male osteoporotic patients study 032	
	S12911 2g	**Placebo**
N	173	87
PT	284	154
n(%)	17 (9.8)*	6(6.9)*
PY	59.9	39.0
OR [95% CI]	1.47 [0.56; 3.88]	
p-value	0.432	

N: Number of patients, PT: Number of patient-years by group
*n: Number of patients with at least one emergent AE IHD, %: (n/N)*100*
PY: Number of patients with at least one emergent AE IHD per 1000 patient-years
OR: odds ratio and CI: Confidence Interval
P value associated to treatment effect: chi-square
**: of note among the 17 patients presented with IHD, 2 patients in the Strontium ranelate group versus 0 in the placebo group presented with blood creatine phosphokinase increased for which the cardiac origin was not established*

As the background history with regard to ischaemic heart disease, cardiac arrhythmias and glucose metabolism disorders was unbalanced between Strontium ranelate and the placebo group an analysis adjusting for these medical histories was performed: The relative risk of ischaemic heart disease in the SR group compared to the placebo group was not significantly increased with HR= 1.24 [0.49; 3.17].

The post-marketing surveillance in males is still very limited.

Osteoarthritis patients:

The overall incidence of cardiac disorders was similar in the 3 groups (5.5%, 5.7% and 5.8% respectively). However, the number of cardiac disorders classified as severe, serious, leading to study drug withdrawal and considered as treatment related were higher in the Strontium ranelate groups.

The CL CL3-12911-018 study report has been submitted by the MAH in a type II variation application:
Table 5. Serious emergent adverse events in the safety set (reported in more than 1 patient in any group) source: table (12.2.1.1)2 in CL3-12911-018 study report)

System organ class Preferred term	SrRan 2g (N=564)			Placebo N=556)		
	NEAE	N	%	NEAE	n	%
Cardiac disorders	**19**	**15**	**2.7**	**7**	**6**	**1.1**
Atrial fibrillation	3	3	0.5	3	3	0.5
Acute myocardial infarction	2	2	0.4	-	-	-
Angina Pectoris	2	2	0.4	-	-	-
Coronary artery disease	2	2	0.4	-	-	-
Acute coronary syndrome	2	2	0.4	-	-	-
Angina unstable	2	2	0.4	-	-	-

Evaluation of risks and new information

The clinical placebo controlled studies involve over 4000 patients treated with strontium ranelate. In post-menopausal osteoporotic patients, the risk of myocardial infarction was significantly higher in the

strontium ranelate treated patient (based on comparisons of events / patient years) compared to placebo, OR 1.6 (1.07-2.38). Findings from the smaller study populations, male osteoporotic patients and osteoarthritis patients give some support for an increased risk of ischemic heart disease in strontium ranelate treated patients.

These data raise concern regarding cardiovascular safety beyond the already recognized risk for VTE. Thus, there is a need for further data presentation and evaluation of cardiovascular safety and its impact on the benefit/risk balance.

A summary of all cardiac safety results across all post menopausal osteoporosis studies, the OSA population, osteoporotic men and osteoarthritis populations should be presented, both as observed frequencies and as events /patient years. In addition to a presentation of all cardiac disorders, the data should also be analyzed as per the following SMQ: myocardial infarctions/ ischemic heart disease, cardiac arrhythmia, as well as embolic and thrombotic events.

The MAH was requested to discuss further the need for risk minimization measures, and how this should affect the RMP.

Characterisation of risks

Important identified risks

Venous Thromboembolic events

Source of the new information:

- Post-marketing surveillance: An increase of the incidence of VTE and pulmonary embolism was observed during the period covered by this PSUR in post-marketing surveillance.

- Data from benefit/risk evaluation (article 20) April 2012: Reinforcement of precautions for use and risk factors with a new contraindication for patient with past history of VTE or immobilization and a warning for patients over 80 years at risk of VTE.

1) In clinical trials

- **Post-menopausal osteoporotic patients**

The VTE incidences, with 95 % CI in the different sets analysed are presented in the table below:

	OSA 2011		OSA in patients with age ≥80		Long term 2 g
	S1291□ 2g	Placebo	S12911 2g	Placebo	
N	3803	3769	761	780	5819
PT	11269.6	11250.1	000.3	2070.1	19765.5
n(%)	89 (2.3)	65 (1.7)	34 (4.5)	19 (2.4)	145 (2.5)
□Y	7.9	5.□	1□.0	9.2	7.3
OR [95% CI]	1.37 [0.99;1.89]		1.87 [1.06;3.31]		
p-value	0.057*		0.029**		

N: Number of patients, PT: Number of patient-years by group
*n: Number of patients with at least one emergent AE VTE, %: (n/N)*100*
PY: Number of patients with at least one mergent AE VTE per 1000 patient-years

- **Male osteoporotic patients**

In the study CL3-12911-032, 3 patients (1.7%) out of 173 presented with VTE in the Strontium ranelate group: a deep vein thrombosis of the lower limb for 2 patients and a suspected pulmonary embolism in 1 patient *versus* none in the placebo group (n = 87). The annual incidence in the Strontium ranelate group was 1.1%.

- **Osteoarthritis patients**

In osteoarthritis studies, 3 patients (0.5%) out of 586 presented with VTE in the Strontium ranelate group: 2 pulmonary embolism and 1 deep vein thrombosis *versus* 1 patient (0.2%) in the placebo group (n=577) with both deep vein thrombosis of the lower limb and a p ulmonary embolism. The annual incidence in the Strontium ranelate group was 0.2 %.

2) In Post-Authorisation study

In the cohort study (CLE-12911-021), among 12 076 patients, 65 VTE were reported in 55 patients (0.46%), giving an annual incidence of 2.1/1000 PY. The VTEs were as follows: deep vein thrombosis (38 patients, 0.32%), pulmonary embolism (23 patients, 0.19%) which account for 35.4% of VTEs (23/65), retinal vein occlusions (2 patients, 0.02%), and venous thrombosis (1 patient, 0.01%). Among these patients, 9 had pulmonary embolism in association with deep vein thrombosis and one patient reported 2 venous thrombosis.
Of note: serious and related cases of this study are also included in the estimated incidence in post-marketing surveillance.

3) In post-marketing surveillance

During the post-marketing experience, 548 events related to "VTE" were reported in 461 patients representing an estimated incidence of 14.2 for 100 000 PY. The incidence of VTE during the period of this report was 16.8/100 000 PY. The reported incidence of VTE is described in the following table:

PSUR period	N patients	Interval reported incidence *	Cumulative reported incidence*
Sep 04 / Mar 05	3	0,57	
Mar 05 / Sep 05	5	0,23	0.29
Sep 05 / Mar 06	14	0,23	0.25
Mar 06 / Sep 06	22	0,22	0.23
Sep 06 / Mar 07	32	0,22	0.22
Mar 07 / Mar 08	65	0,17	0.20
Mar 08 / Sep 08	38	0,16	0.19
Sep 08 / Mar 09	35	0,16	0.18
Mar 09 / Sep 09	33	0,12	0.17
Sep 09 / Mar 10	31	0,11	0.16
Mar 10 / Sep 10	22	0,07	0.15
Sep 10 / Sep 11	68	0,10	0.14
Sep 11 / Sep 12	92	0.17	0.14

And increased VTE risk associated with Strontium ranelate treatment was identified from clinical studies. Following the 2012 European review of Strontium ranelate performed under the Article 20 of the regulation and in order to reduce the risk of VTE, the existing precautions for use were strengthened. Use of Strontium ranelate is now contraindicated in patients with current or previous VTE, as well as in permanently or temporarily immobilized patients. A DHPC circulated to relevant prescribers to inform them of this new contraindication. In order to check the effectiveness of the contra-indication a prescription survey will be carried out.

Hypersensitivity reactions

Source of the new information:

- Post-marketing surveillance: a higher occurrence of severe skin hypersensitivity reactions such as SJS and TEN was observed in Asians as compared to non-Asians.

- Regulatory Authorities: The Singapore Health Sciences Authority issued an alert to healthcare professionals in August 2011 in relation to the occurrence of suspected serious skin reactions associated with Strontium ranelate locally. On 13 July 2012, HSA in Singapore alerted healthcare professionals on the increase in the number of local reports of serious skin reactions suspected to be associated with Strontium ranelate.

Post-marketing surveillance has identified the rare occurrence of hypersensitivity syndromes such as DRESS, SJS and TEN leading to an Urgent Safety Restriction (USR) in November 2007, an update of the SmPC and of the RMP.

No cases of DRESS, SJS or TEN have been reported in the clinical studies database (derived from clinical trials and an observational cohort study) from a total of 18 703 treated patients. To ensure appropriate assessment of all suspected hypersensitivity reactions, an independent Expert Committee was therefore established by the MAH since April 2008 in order to evaluate all past and future potential cases of hypersensitivity skin reactions including DRESS, SJS, and TEN in patients treated with Strontium ranelate.

During the period covered by this report, a higher occurrence of severe skin hypersensitivity reactions such as SJS-TEN was observed in Asians as compared to non-Asians in the cumulative analysis of such events.

During the PSUR period:

- 9 cases of SJS were reported including 6 from patients in Asian countries: out of these 9 cases, the diagnosis of SJS was confirmed by the Expert Committee in 7 patients, including 6 patients from Asian countries.

- No cases of TEN were reported but 1 case (non-Asian case) reported as SJS was confirmed as TEN by the Expert Committee after the data lock point.

The overall number of SJS-TEN reported in the Pharmacovigilance database from all countries and Asian countries in addition to their evaluation by the Expert Committee are presented in the table below.

Table (16.3.2.2) 1 - Cumulative review of SJS and TEN reported in the Asian* population and evaluated by the Expert Committee.

	21-09-2004 to 21-09-2011		PSUR 13 period		Cumulative review from MA 21-09-2004 to 21-09-2012	
	Cases reported in PV database	EC confirmed cases	Cases reported in PV database	EC confirmed cases	Cases reported in PV database	EC confirmed cases Cumulative review
SJS (Asia)	5	4	6	6	11	10
SJS (Total)	17	9	9	7	26	16
SJS Asia* / SJS total (%)	29.4	44.4	66.7	85.7	42.3	62.5
TEN (Asia)	3	3	0	0	3	3
TEN (Total)	7	4	1	1	8	5
TEN Asia* / TEN total (%)	42.9	75.0	0	0	37.5	60.0
SJS + TEN (Asia)	7*	7	6	6	13*	13
SJS + TEN (Total)	22**	13#	9*	8	31***	21#
Case nb Asia* / Total (%)	**31.8**	**53.8**	**66.6**	**75.0**	**41.9**	**61.9**

Asia: Singapore, Taiwan, Hong Kong, Malaysia and Indonesia
** including 1 case with both SJS and TEN coded*
*** including 2 cases with both SJS and TEN coded*
**** including 3 cases with both SJS and TEN coded*
 # one case of SJS + TEN: counted as SJS

When focusing on patients from Asian countries, during the period covered by this PSUR, the proportion of SJS-TEN cases increased, compared to worldwide cases.

In terms of frequency worldwide, the reported case incidence of SJS-TEN from spontaneous reporting is 1 per 154 081 PY of treatment in September 2012 categorising this event as very rare.

In non-Asian countries, the global incidence is 1 per 394 198 PY while in Asian countries the incidence is 1 per 6 316 PY of treatment categorising SJS and TEN events as rare. This data confirms a trend towards an increased frequency of severe skin hypersensitivity reactions such as SJS and TEN in Asian populations compared to non-Asian countries.

Post-marketing surveillance has identified the rare occurrence of hypersensitivity syndromes such as DRESS, SJS and TEN with Strontium ranelate. A higher occurrence of severe skin reactions was observed in Asians in 2011-2012. The section 4.4 of the Strontium ranelate SmPC has been updated with the precaution in patients of Asian origin. A type II variation was approved on 23 October 2012 (European Commission Decision).

Hepatobiliary disorders

No new relevant safety information emerged during the reporting interval of the PSUR in term, frequency or seriousness regarding "hepatitis".

In clinical studies, results were quite similar in the Strontium ranelate group and the placebo group. Few cases of patients reported ASAT and / or ALAT elevation > 3ULN in bothgroups.

In post marketing surveillance:

- 171 spontaneous reports concerning "Drug induced hepatitis" were reported, representing an estimated incidence of 0.05/1000 PY. The estimated incidence of hepatic disorders remains stable over time. A majority (70%) had a favourable outcome. In 11 cases (6.4%), fatal outcome was reported (including 8 cases in a context of severe skin hypersensitivity reaction).

- Among these 171 cases, 79 patients experienced transaminases increase > 3ULN and/or at least one of the following events (as reported): hepatitis (all types), hepatic failure, drug induced liver injury, hepatic necrosis, hepatotoxicity, liver injury. This represents an estimated incidence of 0.02/1000 PY.

Out of them:

-55 patients (69.6%) presented either relevant medical history or relevant context (39 DRESS, 2 acute viral hepatitis A or E and 14 patients with other relevant medical history such as hepato-biliary disorders or cancer) and 24 patients (30.4%) had no medical history and no relevant context (including 18 patients treated by concomitant treatments known to induce liver disorders).

-4 patients (2.3%) presented an hepatic failure (2) or prothrombin< 50% (2). A context of DRESS was reported in these 4 cases. No cases of encephalopathy were reported.

-A majority (75 %) had a favourable outcome. In 9 cases (11%), fatal outcome was reported (all in a context of severe skin hypersensitivity reaction), including one reported during the PSUR period (context of DRESS).

Thus, in post marketing surveillance, cases were reported especially in association with hypersensitivity reactions. Increased serum transaminase (in association with hypersensitivity skin reactions) and hepatitis were added in the undesirable effects section of the SmPC. These type of events remains under close monitoring.

"Hepatobiliary disorders" is refeclted in the SmPC. No new safety actions regarding the risk of hepatobiliary disorders are requested in this PSUR procedure.

Blood cytopenic disorders: bone marrow failure

Post-menopausal osteoporotic patients:

The seriousness and outcome of EAE "blood cytopenic disorders" in OSA 2011 and in Long Term 2g are presented in the table hereafter:

	OSA 2011		Long term 2 g
	S12911 2g	Placebo	
N	3803	3769	5819
n(%)	129 (3.4)	133 (3.5)	239 (4.1)
NEAE	141	147	275
Serious (%)	11 (7.8)	7 (4.8)	17 (6.2)
WEAE	8 (5.7)	4 (2.7)	8 (2.9)
Outcome			
Recovered	67 (47.5)	78 (53.1)	121 (44.0)
Improvement	10 (7.1)	15 (10.2)	29 (10.6)
Not recovered	60 (42.6)	51 (34.7)	117 (42.6)
Fatal	3 (2.1)	1 (0.7)	4 (1.4)
Unknown	1 (0.7)	2 (1.4)	4 (1.4)

Data are expressed as number of emergent events and corresponding percentage

Male osteoporotic patients

In the study CL3-12911-032, the 13 EAE "blood cytopenic disorders" in the strontium ranelate group were non serious and did not lead to treatment discontinuation (except for 1 case), 8 (61.5%) were

recovered. The 4 EAE "blood cytopenic disorders" in the placebo group did not lead to treatment discontinuation, 3 (75.0%) recovered. There was no fatal case.

According to the MAH, no new relevant safety information emerged during the reporting interval of the PSUR in term, frequency or seriousness regarding "bone marrow failure". Bone marrow failure was added in section 4.8 of the SmPC further to the assessment of the PSUR 10 21 February 2011. No new relevant safety information emerged during the reporting interval of the PSUR in term, frequency or seriousness regarding "bone marrow failure". These events will remain under close monitoring.

In a bone biopsy study CL3-12911-025 (described in chapter 2.3.5, submitted and assessed within FUM 021) lymphoid nodes in the bone marrow were reported in 20 patients (9.7%) in the Strontium ranelate group *versus* 1 patient (0.9%) in the alendronate group. Those lymphoid nodes were mostly isolated and of normal type and size. However, no relevant finding in favour of blood cytopenic disorder or bone marrow failure or lymphoproliferative disorder or auto immune disease was evidenced in any of the 21 patients with lymphoid nodes on their post-baseline biopsy.

Bone marrow failure is in the SmPC. No new safety actions regarding the risk of blood cytopenic disorders are requested in this PSUR assessment.

Seizures

Post-menopausal osteoporotic patients

The incidence of serious cases, treatment withdrawal and outcome in the OSA 2011 and in the Long Term 2 g are presented in the table thereafter:

	OSA 2011		Long term 2 g
	S12911 2 g	Placebo	
N	3803	3769	5819
n(%)	12 (0.3)	2(0.05)	18 (0.3)
NEAE	13	4	19
Serious	7(53.9)	1 (25.0)	9(47.4)
WEAE	1(7.7)	2 (50.0)	2(10.5)
Outcome			
Recovered	9(69.2)	3(75.0)	10(52.6)
Improvement	1(7.7)	1(25.0)	1(5.3)
Not recovered	2(15.4)	0	7(36.8)
Fatal	1(7.7)	0	1(5.3)

WEAE: Withdrawal Emergent Adverse Event - NEAE: Number of emergent adverse events

5/12 patients with seizures in the OSA Strontium ranelate group were >80 years old vs none in the placebo group.

Male osteoporotic patients

In the study CL3-12911-032, the seizure case in the placebo group was recovering.

• **Osteoarthritis patients**

According to MAH, No patient experienced any emergent seizure, in osteoarthritis studies.

Seizures are labeled. No new safety actions regarding the risk of seizures are requested in this PSUR assessment.

Disturbance in consciousness

Post-menopausal osteoporotic patients

The incidence with 95% CI in the OSA 2011 and Long term 2 g are presented in the table below:

	OSA 2011		Long term 2 g
	S12911 2 g	Placebo	
N	3803	3769	5819
PT	11269.6	11250.1	17765.5
n (%)	117(3.1)	100(2.7)	190(3.3)
PY	10.4	8.9	9.6
OR [95% CI]	1.16[0.89; 1.53]		
p-value	0.271		

N: Number of patients, PT: Number of patient-years by group
*n: Number of patients with at least one emergent AE disturbances in consciousness, %: (n/N)*100*
PY: Number of patients with at least one mergent AE disturbances in consciousness per 1000 patient-years
Estimate of the overall treatment effect (Mantel-Haenszel estimate): OR: odds ratio and CI: Confidence Interval
p-value associated to the overall treatment effect

Male osteoporotic patients

In the study CL3-12911-032, 4 patients (2.3%) out of 173 presented with disturbances in consciousness in the Strontium ranelate group versus 2 (2.3%) out of 87 in the placebo group. The annual incidence was 1.4% in the Strontium ranelate group.

• Osteoarthritis patients

In osteoarthritis studies, 9 patients (1.5%) out of 586 experienced disturbances in consciousness in the Strontium ranelate group versus 6 (1.0%) out of 577 in the placebo group. The annual incidence was 0.7 % in the Strontium ranelate group.

2) In post-Authorisation study

In the cohort study, among 12 076 patients, 27 cases of disturbances in consciousness were reported in 27 patients (0.22 %). Among these, 8 events were considered as related to treatment by investigator.

Of note: serious and related cases of this study are also included in the estimated incidence in post-marketing surveillance.

3) In post-marketing surveillance

During the post-marketing experience, 165 events related to "Disturbance in consciousness" were reported in 156 patients representing an estimated incidence of 4.8/100 000 PY. Among them, 34 events "syncope" and 15 events "loss of consciousness" were reported in 48 patients (one patient experienced both events) which represents an estimated incidence of 1.5/100 000 PY.

No new relevant safety information emerged during the reporting interval of the PSUR in term, frequency or seriousness regarding Disturbance in consciousness.

Disturbance in consciousness is labeled. No new safety actions regarding the risk of Disturbance in consciousness are requested in this PSUR assessment.

CK increase and musculoskeletal disorders

It is proposed to not consider any longer this identified risk as important.

No muscular toxicity or biological abnormalities were observed in any of the non-clinical studies performed.

- In clinical studies CK elevation is usually light and is not associated with clinical symptoms and the increase in CK doesn't involve the cardiac fractions of CK (CPK MB).

In addition, CK elevation disappears in most cases without changes in the treatment.

- In post marketing surveillance, most of the cases were not serious and the reported incidence remains stable (1.4/100 000 PY).

- No related mechanism has been isolated to explain the CK elevations.

Insomnia

It is proposed to not consider any longer this identified risk as important.

Strontium ranelate had no behavioural effects, nor did influence hexobarbital-induced sleep in the non-clinical studies.

- In clinical studies no case was serious and the study drug was maintained in most of cases (> 90%).

- In post marketing surveillance, most of the cases were not serious and the reported incidence remains stable (4.0/100 000 PY).

Confusion

It is proposed to not consider any longer this identified risk as important. Strontium ranelate had no behavioural effects, no CNS toxicity nor CNS accumulation demonstrated with Strontium ranelate in the non-clinical studies.

- In clinical studies the percentage of severe cases in the Strontium ranelate group was lower than in the placebo group.

- In post marketing surveillance, the majority of the cases were not serious and the reported incidence remains stable (2.7/100 000 PY).

Memory loss

It is proposed to not consider any longer this identified risk as important.

No CNS toxicity or CNS accumulation demonstrated with Strontium ranelate in nonclinical studies.

- In clinical studies the percentage of severe memory loss in the Strontium ranelate group was lower than in the placebo group.

- In post marketing surveillance, most of the cases were not serious and the reported incidence remains stable (6.1/100 000 PY).

The MAH proposed to not consider any longer the following identified risk as important: memory impairment, musculoskeletal disorders, confusion and insomnia. These risks are all labeled and there is no new safety signal. The MAH conclusions are endorsed by the PRAC.

Hypertension

It is proposed to not consider any longer this potential risk "hypertension" as important.

- In clinical studies in post-menopausal osteoporosis, the percentage of patients with hypertension was 18.6% and 16.9% respectively in the Strontium ranelate and placebo groups (OR [95%CI] = 1.12 [1.00-1.27], p =0.055) with a percentage of severe cases comparable in the Strontium ranelate group than in the placebo group (9.3% versus 8.6%). In men with osteoporosis in the CL3-12911-032 study the incidence of hypertension was similar in the Strontium ranelate and in the placebo group after 2 years of treatment (11.6% versus 13.8%). No significant difference was observed regarding the values of arterial pressure in clinical trials.

- Over the 96-month period of post marketing surveillance, one hundred and thirty eight (138) events were reported, 61 (44.2%) were serious. The reported incidence of Hypertension remains stable overtime at 0.04 per 1000 PY. In addition, hypertension events were associated with confounding factors.

Hypertension prevalence is strongly correlated with stroke mortality and more modestly with total Cardiovascular Disorders (Wolf-Maier, 2003). However, in clinical studies in PMO women, although a higher percentage of patients reported hypertension in the Strontium ranelate group compared to the placebo group, the incidence of stroke (SMQ Ischemic Cerebrovascular Condition narrow) was similar in both groups with an OR [95% CI] of 1.04 [0.84; 1.28] as was the incidence of stroke leading to death (0.35% versus 0.25% in the Strontium ranelate and the placebo groups respectively). In addition, in the same population, the overall incidence of cardiovascular deaths (2.1% in both groups) as well as the incidence of cardiac deaths (0.9% versus 0.8%) was similar in both groups.

Similarly, in post-marketing surveillance, out of the 138 cases of hypertension:

- One patient with a medical history of hypertension experienced an ischaemic cerebrovascular event (transient ischaemic attack) concomitant with blood pressure increased.

- One patient with a medical history of hypertension experienced an event related to myocardial infarction: "troponin T increased" associated with blood pressure increased in a context of SJS.

The PRAC did not support the MAH's proposal to consider hypertension as not important potential risk. In clinical studies in PMO women, a higher incidence of myocardial infarction in strontium ranelate treated patients compared to placebo. As hypertension correlates with cardiovascular disorders, this potential risk is still considered important.

Signals rejected as refuted signals:

Intestinal nephritis

Source of the signal: The signal "Interstitial nephritis" was considered as validated following the evaluation of the PSUR 9 and based on data from post-marketing experience. Among the 8 cases of "Nephritis" (2) and "Tubulointerstitial nephritis" (6) reported from marketing authorization to 21 June 2012, the causality was assessed as "doubtful" in 7/8 cases. In the only one case assessed as possible the event occurred in a context of DRESS. Overall, in 6/8 patients (75%), the event occurred in a context of hypersensitivity.

In the clinical studies and in the post authorization study, no case of interstitial nephritis in the Strontium ranelate group was reported. No safety concerns were identified from all other available sources. The overall estimated incidence of "interstitial nephritis" remains stable and low overtime: 0.3/100 000 PY up to 21 September 2011 (PSUR 12) versus 0.2/ 100 000 PY up to 21 September 2012 (PSUR 13).

The conclusion by the MAH to consider intestinal nephritis as a false signal is not supported by the PRAC and these serious events should continue to be closely monitored and remain as a potential risk for strontium ranelate in the RMP.

Hallucination

Source of the signal: The signal "Hallucination" was considered as validated following the request from Regulatory Authorities to closely monitor this event further to PSUR 7 assessment and based on data from post-marketing experience.

Among the 11 cases of "Hallucination" reported from marketing authorization to 21 June 2012, the causality was assessed as "doubtful" in all the cases and no medical investigations were performed in any case. In 91% of the cases, the event could be explained by patient's medical history, relevant context or concomitant medications known to induce this kind of events. In 4/11 cases (36%), another drug was also suspected. All the events had a favourable outcome and no fatal outcome was reported. No safety concerns were identified from all other available sources.

The signal was closed and considered as refuted signal based on data reported from marketing authorization up to 21 June 2012. The overall estimated incidence of "hallucination" remains stable and low overtime: 0.4/100 000 PY up to 21 September 2011 (PSUR 12) versus 0.3/ 100 000 PY up to 21 September 2012 (PSUR 13).

The PRAC endorsed the MAH's conclusion.

Depression

The signal "Depression" was considered as validated following the request from Regulatory Authorities to closely monitor this event further to PSUR 8 assessment and based on data from post-marketing experience.

Among the 51 cases of "Depression" reported from marketing authorization to 21 June 2012, the causality was assessed as doubtful in 92%. Among the 3 cases assessed as "likely", 2 cases were poorly documented. The case assessed as "possible" occurred in a context of DRESS. In 59 % of the cases, the event could be explained by the medical history, relevant context or concomitant treatments known to induce depression.

A majority of the events (56.9%) had a favourable outcome and no fatal case was reported.

No concern was raised from non-clinical studies regarding depression in particular Strontium ranelate had no behavioural effects.

In clinical trials percentages of patients experiencing depression were similar in both groups as well as in the elderly women population.

No safety concerns were identified from all other available sources.

The signal was closed and considered as refuted signal based on data reported from marketing authorization up to 21 June 2012. At this time, 51 cases were reported. Since then, 1 new case of "depression" was reported until the data lock point. The overall estimated incidence of "depression" remains stable overtime: 1.6/100 000 PY up to 21 September 2011 (PSUR 12) versus 1.6/ 100 000 PY up to 21 September 2012 (PSUR 13).

The conclusion by the MAH to consider depression as a false signal is not supported by the PRAC. 21/51 cases occurred within one month after drug intake and the event regression seemed linked to drug withdrawal in 48.9% of the cases. Depression should remain as a potential risk for strontium ranelate in the RMP.

Photosensitivity

Source of the signal: The signal "Photosensitivity" was considered as validated following the request from Regulatory Authorities to closely monitor this event further to PSUR 4 assessment and based on data from post-marketing experience.

Among the 30 cases of "Photosensitivity" reported from marketing authorization to 21 June 2012, the role of Strontium ranelate was assessed as "doubtful" in 29/30 cases and only one case was considered with imputability as likely. In 53 % of the cases, the event could be explained by the medical history, relevant context or concomitant treatments known

Among the 30 cases of "Photosensitivity" reported from marketing authorization to 21 June 2012, the role of Strontium ranelate was assessed as "doubtful" in 29/30 cases and only one case was considered with imputability as likely. In 53 % of the cases, the event could be explained by the medical history, relevant context or concomitant treatments known to induce photosensitivity. No skin biopsy was performed in any cases. Only one patient underwent photobiological examination and patch test: photobiological investigations were negative, drug photosensitivity and polymorphous lucitis were excluded.

A majority of the events (56.7%) had a favourable outcome and no fatal outcome was reported. According to the preclinical studies, no adverse effect of Strontium ranelate in presence of light has been detected during the photosafety evaluation carried out. Under the experimental conditions reported, Strontium ranelate is devoid of any phototoxic potential. Furthermore, in clinical studies, a very few and a similar number of patients experienced photosensitivity disorders in both groups.

No safety concerns were identified from all other available sources. The signal was considered as a false signal.

The signal was closed and considered as refuted signal based on data reported from marketing authorization to 21 June 2012. At this time, 30 cases were reported (including one non serious case from solicited source not presented in the summary tabulation). Since then, no new case of "photosensitivity" was reported until the data lock point. The overall estimated incidence of

"photosensitivity" remains stable and low overtime: 0.9/100 000 PY up to 21 September 2011 (PSUR 12) versus 0.9/ 100 000 PY up to 21 September 2012 (PSUR 13).

The conclusion by the MAH was endorsed by the PRAC.

Pancreatitis

Source of the signal: The signal "Pancreatitis" was considered as validated following the request from Regulatory Authorities to closely monitor this event further to PSUR 2 assessment and based on data from post-marketing experience.

Among the 11 events "pancreatitis" reported from marketing authorization to 21 June 2012, 9 were assessed as serious (2 patients experienced amylase increased and lipase increased assessed as non-serious). The causality was assessed as doubtful in 91% of the events.
The event assessed as "possible" occurred in a context of DRESS. In 7/11 patients (64%), the event could be explained by the medical history or a relevant context. Out of the 4 other patients, "pancreatitis" was reported less than 24h after Strontium ranelate initiation in 1 patient, 2 patients were not hospitalized and no investigation were performed and the diagnosis of pancreatitis was confirmed by CT Scan in the last patient. A majority of the events (81.8%) had a favourable outcome and no fatal case was reported.

No safety concerns were identified from all other available sources.

The signal was closed and considered as refuted signal based on data reported from marketing authorization to 21 June 2012. At this time, 11 cases were reported. Since then, no new case of "pancreatitis" was reported until the data lock point. The overall estimated incidence of "pancreatitis acute" remains stable and low overtime: 0.3/100 000 PY up to 21 September 2011 (PSUR 12) versus 0.3/ 100 000 PY up to 21 September 2012 (PSUR 13).

The conclusion by the MAH to consider pancreatitis as a false signal is not supported by the PRAC and these serious events should continue to be closely monitored and remain as a potential risk for strontium ranelate in the RMP.

Bone sarcoma

Source of the signal: The signal "bone sarcoma" was considered as validated following the request from Regulatory Authorities to closely monitor this event further to PSUR 8 assessment and based on data from post-marketing experience.

Two (2) cases of bone sarcoma were reported from post marketing surveillance including 1 case inadequately documented. One Ewing's sarcoma was reported in the cohort study but the event was not related to the treatment by the investigator.

No case was reported in any clinical studies. No safety concerns were identified from all other available sources.

The signal was closed and considered as refuted signal based on data reported from marketing authorization to 21 June 2012. At this time, 2 cases were reported. Since then, no new case of "bone sarcoma" was reported. The overall estimated incidence of "bone sarcoma" remains stable and very low overtime: 0.07/100 000 PY up to 21 September 2011 (PSUR 12) versus 0.06/ 100 000 PY up to 21 September 2012 (PSUR 13).

The conclusion by the MAH to consider bone sarcoma as a false signal is not supported by the PRAC. As these malignancies are extremely rare, this event should remain closely monitored and should remain as a potential risk for strontium ranelate.

Weight increased

Source of the signal: Spontaneous event reports from post-marketing experience. A total of 106 cases were reported from marketing authorization until 21 June 2012. The causality was doubtful in 95% of the cases. The mean weight gain of these cases was 4.5 kg.

The overall estimated incidence of "weight increased" remains stable overtime: 3.5/100 000 PY up to 21 September 2011 (PSUR 12) versus 3.4/ 100 000 PY up to 21 September 2012 (PSUR 13). The signal was closed and considered as refuted signal based on data reported from marketing authorization to 21 June 2012. This event will continue to be closely monitored through the signal detection process.

The PRAC endorsed the MAH's conclusion.

Fatigue

Source of the signal: Spontaneous event reports from post-marketing experience

Among the 257 cases of "fatigue" and "asthenia" reported from marketing authorization, the causality was assessed as doubtful in 95% of the cases. The 3 cases assessed as "possible" occurred in a context of DRESS. Among the 10 cases assessed as "likely", the event could be explained by a relevant context (musculoskeletal pain (3), gastric disorders (3) and headache (1)) or concomitant treatments likely to induce fatigue (5 cases) in 8 cases. In most of the cases (87.6%), the event could be explained by the medical history, relevant context or concomitant treatments known to induce fatigue.

The overall estimated incidence of asthenia and fatigue remains stable overtime: 7.7/100 000 PY up to 21 September 2011 (PSUR 12) versus 8.0/ 100 000 PY up to 21 September 2012 (PSUR 13). No safety concerns were identified from all other available sources.

The conclusion by the MAH to consider fatigue as a false signal is not supported by the PRAC. 123/257 cases occurred within one month after drug intake and the event regression seemed linked to drug withdrawal in 59% of the cases. Fatigue should remain as a potential risk for strontium ranelate in the RMP.

Eye disorders

Source of the signal: In the CL3-12911-030 study there was an overrepresentation of eye disorders and cataract in Strontium ranelate treated patients versus alendronate treated patients.

Consequently, an analysis of all the cases of eye disorders and cataract in post-marketing and clinical trials was performed.

In a large 3-year post marketing observational cohort having included 12076 patients with a mean follow During the post-marketing surveillance, 212 non listed eye disorders were reported including 2 cases of cataract not highlighted by the reporter and assessed as doubtful. The analysis focused on the most reported unlisted events (118 events including blurred vision, eye irritation, eye pain, conjunctival disorders, visual impairment) the causality was assessed as doubtful in 89% of the cases. The 6 cases assessed as "possible" occurred in a context of listed severe hypersensitivity reaction.

Among the 7 cases assessed as "likely", the event could be explained by a relevant context (geriatric vitreous opacity, dizziness, and headache) in 4 cases. Overall, in a large number of cases (59.3%) the event could be explained by the medical history or relevant context known to induce eye disorders. The other events from the SOC "Eye disorders" were isolated (less than 10 events reported) and did not constitute a new safety signal.

No signal was shown in up duration of 32 months.

In the study CL3-12911-030, eye disorders were present in 15.4% of patients in the Strontium ranelate group versus 3.2% in the alendronate group. This difference was mainly due to cataract that was more frequent in the Strontium ranelate group (9 patients, 9.9%) than in the alendronate group (2 patients, 2.1%). It is of note that medical history of eye disorders was unbalanced between the two groups at baseline, 32.3% in the S12911 group versus 9.4% in the alendronate group, and for cataract 20.4% versus 5.2%. Following the assessment report of the CL3-12911-030 study, further analysis of eye disorders and cataract were performed in OSA 2011 post-menopausal women: overall, events within the SOC Eye disorders were reported in 12.6 % patients in the Strontium ranelate group and 13.3% in the placebo group, and considering the HLT Cataract conditions in 6.7% and 7.4 % patients. In conclusion, no increased incidence of eye disorders or cataract was detected in clinical trials and results observed in study CL3-12911-030 are likely due to the difference already present at baseline. The signal was considered as a false signal and the event will continue to be closely monitored through the signal detection process.

The conclusion by the MAH is endorsed by the PRAC.

Drug interactions with anticoagulants

Souce of the signal: The signal "drug interaction with anticoagulants" was considered as validated following the request from Regulatory Authorities to closely monitor this event and based on data from post-marketing experience. To effectively monitor the possible drug interaction between Strontium ranelate and oral anticoagulant drugs, "Drug interaction" was coded in all cases in which the patient treated with Strontium ranelate and an anticoagulant drug experienced an INR fluctuation.

From post marketing experience, 14 cases of drug interactions with anticoagulants were reported. In most of the cases, the patient had a concomitant treatment known to increase oral anticoagulant effect. The overall estimated incidence of drug interactions with anticoagulants remains stable overtime: 0.4/100 000 PY up to 21 September 2011 (PSUR 12) versus 0.4/100 000 PY up to 21 September 2012 (PSUR 13).

No information could be obtained from other sources. The signal was considered as a false signal and the event will continue to be closely monitored through the signal detection process.

The conclusion by the MAH is endorsed by the PRAC.

Signals categorized as identified not important risk:

Malaise

Among the 123 cases of "Malaise" reported from marketing authorization until 21 March 2012, the event regression seemed linked to drug withdrawal (positive dechallenge) in 56.1% of the cases. In 8 cases a positive rechallenge was reported including 3 serious cases.

The overall estimated incidence of "malaise" reported from post-marketing experience tends to increase: 3.4/100 000 PY up to 21September 2011 (PSUR 12) versus 4.2/ 100 000 PY up to 21 March 2012.

Based on the above arguments and in view of the large number of cases received from postmarketing experience, the MAH decided to update the section 4.8 of the SmPC (type 2 variation approved by European commission on 23 October 2012).

The MAH concluded that the signal could be cathegorised as non-important identified risk.

28/121 events of "malaise" were considered serious and 9% not recovered. The PRAC was of the view that this signal is still considered important.

Paraesthesia

Among the 121 cases of "paraesthesia", "burning sensation", "dysaesthesia", "hypoaesthesia", "skin burning sensation" and "formication" reported from marketing authorization to 21 March 2012, the event regression seemed linked to drug withdrawal (positive dechallenge) in 38.8% of the cases. In 11 cases, a positive rechallenge was reported including 7 cases in which the patient had no medical history or relevant context likely to induce or favour paraesthesia. Overall, in 41% of the cases, the patient had no medical history or relevant context likely to induce or favour paraesthesia.

Based on the above arguments and in view of the data received from post-marketing experience, the MAH decided to update the section 4.8 of the SmPC (type 2 variation approved by European commission on 23 October 2012).

The MAH concluded that the signal could be cathegorised as non-important identified risk.

23/121 events of "paraesthesia" were considered serious, 22% not recovered. The PRAC was of the view that this signal is still considered important.

Dry mouth

Among the 58 cases of "dry mouth" reported from marketing authorization until 21 March 2012 the event regression seemed linked to drug withdrawal (positive dechallenge) in 36.2% of the cases. In the 3 cases with a positive rechallenge, the patient had no medical history or relevant context likely to induce or favour dry mouth. Overall, in 71 % of the cases, the patient had no medical history or relevant context of concomitant treatments likely to induce or favour dry mouth.

Based on the above arguments and in view of the data reported from post-marketing experience, the MAH decided to update the section 4.8 of the SmPC (type 2 variation approved by European commission on 23 October 2012).

Conclusion: Signal categorized as non-important identified risk.

Only 3/58 of the events "dry mouth" events were considered serious. The conclusion by the MAH to cathegorise this signal as non-important identified risk is endorsed by the PRAC.

Vertigo

Among the 60 cases of "vertigo" reported from marketing authorization until 21 March 2012, the event regression after the drug withdrawal (positive dechallenge) occurred in 29 cases (48.3%). In 2 cases assessed as likely, a positive rechallenge was reported including 1 case in which the patient had no medical history or relevant context likely to induce or favour vertigo. In the case assessed as possible, no medical history or relevant context likely to induce or favour vertigo was reported.

Based on the above arguments and in view of the data reported from post-marketing experience, the MAH decided to update the section 4.8 of the SmPC (type 2 variation approved by European commission on 23 October 2012).

The MAH concluded that this signal could be categorized as non-important identified risk.

23/121 events were considered serious and 15% not recovered. The signal is still considered important by the PRAC.

Dizziness

Among the 158 cases of "dizziness" reported from marketing authorization until 21 March 2012, the event regression seemed linked to drug withdrawal (positive dechallenge) in 50.6% of the cases. In 11 cases, a positive rechallenge was reported including 5 cases in which the patient had no medical history or relevant context likely to induce or favour dizziness.

Based on the above arguments and in view of the data reported from post-marketing experience, the MAH decided to update the section 4.8 of the SmPC (type 2 variation approved by European commission on 23 October 2012).

The MAH concluded that this signal could be categorized as non-important identified risk.

31/158 events were considered serious and 9.5% were not recovered**.** The signal is still considered important.

Conclusion on signal and risk evaluation

Data presented in the PSUR raise concern regarding cardiovascular safety beyond the already recognized risk for VTE. Thus, there is a need for further data presentation and evaluation of cardiovascular safety and its impact on the benefit/risk balance.

In the previous PSUR, the following events were considered by the MAH as potential risks: "interstitial nephritis", "hallucination", "depression", "bone sarcoma", "pancreatitis" and "photosensitivity". However, these events were reassessed according to the definition provided in GVP Annex I-Definitions. Based on a scientific evaluation of all currently available information, the MAH considered these events as "false signals" and proposes to remove them from the potential risk list.

The PRAC agreed with the MAH proposal to remove "hallucination" and "photosensitivity". However, the PRAC considered that "interstitial nephritis", "depression", "bone sarcoma" and "pancreatitis" should remain in the potential risk list.

Memory loss, CK increase and musculoskeletal disorders, confusion and insomnia were considered as important identified risks. It is proposed to no longer consider these risks as important. These risks are all labeled and there is no new safety signal. The MAH conclusions were endorsed by the PRAC.

Hypertension was considered as important potential risk: it is proposed to no longer consider this risk as important. The PRAC did not agree, and requested that hypertension should remain as an important risk.

No new information was provided during the period covered by this report regarding skeletal accumulation of strontium ranelate.

4. Request for supplementary information

4.1. Request for Supplementary Information to be provided in written:

During its March 2013 meeting, the PRAC requested the following supplementary information to be provided in written by the MAH:

In post-menopausal osteoporotic patients, the risk of myocardial infarction was significantly higher in the strontium ranelate treated patient (based on comparisons of events / patient years) compared to placebo, OR 1.6 (1.07-2.38). Findings from the smaller study populations, male osteoporotic patients and osteoarthritis patients give some support for an increased risk of ischemic heart disease in strontium ranelate treated patients. These data raise concern regarding cardiovascular safety beyond the already recognized risk for VTE. Given the thrombotic potential of strontium ranelate, there is a possible mechanistic rationale for a wider cardiovascular risk. Thus, there is a need for further data presentation and evaluation of cardiovascular safety and its impact on the benefit/risk balance.

1. A summary of all cardiac safety results across all post menopausal osteoporosis studies, the OSA population, osteoporotic men and osteoarthritis populations should be presented, both as observed frequencies and as events /patient years. In addition to a presentation of all cardiac disorders, cardiovascular death/sudden death, as well as cerebrovascular disease, the data should also be analyzed as per the following SMQ: myocardial infarctions/ ischemic heart disease, cardiac arrhythmia, as well as embolic and thrombotic events.
2. In addition, it is also of importance to evaluate when the events occur in relation to treatment start. Such data should be presented.
3. The MAH should also discuss further need for risk minimization measures, and how this should affect the RMP.
4. The number of fractures from the efficacy data (both vertebral and non-vertebral) should be summarized and presented for all clinical trials in postmenopausal osteoporosis, OSA population and osteoporotic men.
5. Based on the issues requested above, the MAH should discuss the benefit/risk balance of strontium in the approved indications.

PRAC Question 1: A summary of all cardiac safety results across all post menopausal osteoporosis studies, the OSA population, osteoporotic men and osteoarthritis populations should be presented, both as observed frequencies and as events /patient years. In addition to a presentation of all cardiac disorders, cardiovascular death/sudden death, as well as cerebrovascular disease, the data should also be analyzed as per the following SMQ: myocardial infarctions/ ischemic heart disease, cardiac arrhythmia, as well as embolic and thrombotic events.

Following PRAC request, an extensive review of all cardiac safety data across all population was performed. Results are presented hereafter.

Overall Safety Set (OSA) 2011 2g versus placebo PMO women:

The OSA 2011 PMO women 2gr versus placebo corresponds to the data from 7 randomized studies in postmenopausal osteoporotic patients: 2 phase II studies CL2-004 (Meunier, 2002; NP07869) and CL2-005 (Reginster 2002; NP08511) and 5 phase III studies CL3-009 (Meunier, 2004; NP08338/NP22819), CL3-010 (Reginster 2005; NP08340/NP22824), CL3-013 (Hwang 2008; NP22514), CL3-015 (Liu 2009; NP25026), CL3-017 (NP24357). This set consisted of 7572 patients (3803 patients treated with strontium ranelate vs 3769 patients treated with placebo). No overall safety analysis was performed since 2011 as only results from a small single study (N= 217 randomized patients including 109 patients in the SR group) became available. Details of studies included in the OSA are provided in Table 2.

Table 2 - OSA2011- PMO women- description of studies population

Studies	Type of study/study objective	Number of patients by treatment group S12911 2g/Placebo	Mean age+/-SD (years) in the S 12911 group	Exposure (days)
CL2-004	To detemine the minimal active dose of strontium ranelate for the curative treatment of established post-menopausal vertebral osteoporosis	87/91	65.[illegible]+/-6.9	671.8(202.1)
CL2-005	To detemine the minimal active dose for prevention of bone loss	56/57	54.2+/-3.2	620.5(255.4)
CL3-009	To assess efficacy in reducing vetebral fractures	826/814	69.6+/-7.2	1137.3(519.8)
CL3-010	To assess efficacy in reducing peripheral fractures	2526/2503	76.7+/-5.0	1177.7(702.5)
CL3-013	To assess efficacy on Lumbar BMD in Tawainese patients	67/65	64.3+/-6.7	351.1(76.9)
CL3-015	To assess efficacy on lumbar BMD in Asian patients (China, Malaysia, Hong Kong)	164/165	67.0+/-6.9	360.2(90.2)
CL3-017	To assess efficacy on lumbar BMD in Korean patients	77/74	64.8+/-6.1	340.2(116.4)

Osteoporotic men

The safety of strontium ranelate 2g daily in men with osteoporosis was assessed in the CL3-032 study, a 2-year double-blind placebo-controlled randomized (randomization 2:1) trial. This set consists of 173 strontium ranelate-treated patients and 87 placebo-treated patients. This study aimed to assess the efficacy in increasing the bone mineral density. The mean age was 72.7+/-5.7 years.

Osteoarthritis population

The safety of strontium ranelate (1g and 2g daily) was assessed in patients with osteoarthritis in the CL3-028 and CL3-018 studies. The study CL3-028 was a 2-year prospective, randomized placebo-controlled. This aimed to assess the effectiveness on algofunctional symptoms on knee osteoarthritis, the mean age was 62.2+/-7.8 years The study CL3-018 study was a 3-year prospective multicentre, international, double-blind, placebo-controlled study. The primary endpoint was the radiographic joint space narrowing of the knee medial tibiofemoral compartment. The mean age was 62.8+/-7.2 years. In overall, this set consists of 586 strontium ranelate-treated patients and 577 placebo-treated patients. In accordance with the current posology in osteoporosis and with the proposed posology in osteoarthritis only safety data related to the 2g dose are assessed.

CARDIAC SAFETY results

Cardiac disorders, cardiovascular mortality, cerebrovascular disease

The risk of cardiac events, cardiovascular mortality, cerebrovascular events was assessed in all populations. Odds ratios are not provided when the number of patients and of events were too small with too large confidence intervals to allow an appropriate interpretation. Results are displayed in table below.

Table 3 - Cardiac disorders, cardiovascular mortality, cerebrovascular events in the three populations (strontium ranelate 2gr versus placebo)

	OSA 2011 (PMO women)		Osteoporotic men (study 032)		Osteoarthritic patients (studies 018 and 028)	
	S12911 2g	Placebo	S12911 2g	Placebo	S12911 2g	Placebo
N	3803	3769	173	87	586	577
PY	11269.6	11250.1	284	154	1244.6	1282.8
SOC Cardiac disorders						
n (%)	645(17.0)	631(16.7)	28(16.2)	12(13.8)	36(6.1)	33(5.7)
Per 1000 PY	57.2	56.1	98.6	77.9	28.9	25.7
OR [95%CI]	1.01 [0.90 ; 1.15]		1.21 [0.58 ; 2.51]		1.08 [0.66 ; 1.76]	
Serious cardiac disorders						
n (%)	262 (6.9)	215 (5.7)	11 (6.4)	4 (4.6)	16 (2.7)	6(1.0)
Per 1000 PY	23.2	19.1	38.7	26.0	12.9	4.7
OR [95%CI]	1.22 [1.02 ; 1.48]					
Cardiovascular events leading to death (including death/sudden death)						
n (%)	80(2.1)	81(2.1)	2(1.2)	1(1.1)	1(0.2)	0(0.0)
Per 1000 PY	7.1	7.2	7.0	6.5	0.8	0.0
OR [95%CI]	0.98 [0.71 ;1.34]					
Death/Sudden death (PT)						
n (%)	18(0.5)	30(0.8)	2(1.2)	0(0.0)	1(0.2)	0(0.0)
Per 1000 PY	1.6	2.7	7.0	0.0	0.8	0.0
OR [95% CI]	0.59 [0.33; 1.06]					
Cerebrovascular disease (SMQ CNS haemorrages and cerebrovascular conditions)						
n (%)	201(5.3)	178	3 (1.7)	10.6	5(0.9)	4.0
Per 1000 PY	195(5.2)	1[illegible]	5(5.7)	32.5	10(1.7)	7.8
OR [95% CI]	1.02[0.83;1.26]					

N: number of patients and number of Patient-Years (PY) by group
n(%) : number of patients with at least one emergent AE
Annual incidence per 1000 PY: number of patients with at least one AE per 1000 patients-year
OR[95%CI]: odds ratio and confidence interval (Mantel-Haenszel estimate for OSA 2011)

The PRAC noted that a consistent numerical increase in serious cardiac disorders was observed in Strontium ranelate treated patients in all treatment groups (PMO women, male osteoporosis and osteoarthritis). No differences were observed in the data for overall cardiac disorders in PMO women, cardiovascular death including death/sudden death and cerebrovascular diseases.

Cardiac disorders (System Organ Class) were similarly reported in the strontium ranelate and placebo groups in postmenopausal osteoporotic patients and in osteoarthritic patients: 17.0% versus 16.7 %, OR [95%CI]: 1.01 [0.9; 1.15] and 6.1% versus 5.7% OR [95%CI]: 1.08 [0.66; 1.76], respectively.

In osteoporotic men (260 patients, 173 and 87 in the strontium ranelate and in the placebo group respectively), the incidence of cardiac disorders was higher in the strontium ranelate group than in the placebo group (16.2% vs 13.8%) over 2 years. The difference, which was not statistically significant (OR: 1.21 [0.58; 2.51]), was mainly due to coronary artery disease (HLGT): angina pectoris (4% vs 0%), myocardial infarction (acute or not) (1.7% versus 1.1%) and myocardial ischemia (1.2% vs 0%) and arrhythmias (SMQ cardiac arrhythmias): 8.7 versus 6.9%. In this study, baseline risks factors for coronary

artery disease were unbalanced between the strontium ranelate and the placebo groups for ischemic heart disease (20.8 versus17.2), cardiac arrhythmias (20.2% versus 11.5%), diabetes (8.1 versus 6.9%) and hypertension (43.9% versus 40.2%).

Serious cardiac disorders were reported in 6.9% and 5.7% of the patients in the strontium ranelate and the placebo groups respectively in the PMO population, in 6.4 versus 4.6% in osteoporotic men and in 2.7 versus 1.0% in osteoarthritis patients. Serious cardiac disorders concern mostly ischemic cardiac events; in PMO women, in both groups, approximately 48% of the serious cardiac adverse events corresponded to ischemic heart disease events (SMQ IHD broad excluding non-specific increase in CPK) while 23% in the strontium ranelate group and 16% in the placebo group corresponded to myocardial infarction (SMQ MI narrow); in osteoporotic men, 82 and 75% respectively in the strontium ralenate and in the placebo groups corresponded to an ischemic heart disease with 27% versus 25% corresponding to a myocardial infarction; in osteoarthritis patients, 62.5% of these events corresponded to an ischemic heart disease with 31.3% corresponding to a myocardial infarction in the strontium ranelate group.

Importantly, no difference was found in the overall cardiovascular mortality including deaths and sudden deaths in any population: 2.1% in both groups in postmenopausal osteoporotic patients, 1.2% in the strontium ranelate group versus 1.1% in the placebo group in osteoporotic men and 0.2 versus 0% in osteoarthritic patients. In the PMO women, overall mortality was similarly reported in both groups (3.8%, 13.0 vs 3.8% 12.6 patient-years, OR 1.2 [0.80, 1.29]).

In PMO women, cerebrovascular diseases (SMQ central nervous system haemorrhages and cerebrovascular conditions) were reported equally in the strontium ranelate 2gr and in the placebo groups (5.3% versus 5.2% respectively). The incidence of cerebrovascular events was lower in the Strontium ranelate than in the placebo group in osteoporotic men (1.7 versus 5.7% respectively) as well as in the osteoarthritis population (0.9% versus 1.7% respectively).

Analysis per SMQ

Cardiac safety data were further analyzed using the following Standard MedDRA Queries (SMQ) defined in the 'introductory guide for SMQ version 14.0': myocardial infarction, ischemic heart disease, embolic and thrombotic events ischemic cerebrovascular conditions as well as cardiac arrhythmias in the PMO women (OSA 2011), in men with osteoporosis and in osteoarthritis.

In addition, as transient emergent increases in creatine kinase (CK) activity from musculo-skeletal origin were reported in patients treated with strontium ranelate (SmPC), an analysis was performed on the SMQ Ischaemic Heart Disease Broad, after having excluded CPK non-specific of cardiac origin in order to stringently reassess the incidence of ischaemic heart disease. Odds ratios are not provided when the number of patients per group and the number of events were too small with too large confidence intervals to allow an appropriate interpretation.

Results are displayed in table below.

Table 4 - Analysis of cardiac safety data per SMQ in the three populations (strontium ranelate 2gr versus placebo)

	OSA 2011 (PMO women)		Osteoporotic men (study 032)		Osteoarthritic patients (studies 018 and 028)	
	S12911 2g	Placebo	S12911 2g	Placebo	S12911 2g	Placebo
N	3803	3769	173	87	586	577
PY	11269.6	11250.1	284	154	1244.6	1282.8
SMQ Myocardial Infarction Narrow						
n (%)	64(1.7)	40(1.1)	3(1.7)	1(1.1)	5(0.9)	1(0.2)
Per 1000 PY	5.7	3.6	10.6	6.5	4.0	0.8
OR [95% CI]	1.6 [1.07; 2.38]					
SMQ Ischaemic Heart Disease Broad excluding CPK non-specific of cardiac origin						
n (%)	325(8.5)	299(7.9)	15(8.7)	6(6.9)	15(2.6)	8(1.4)
Per 1000 PY	28.8	26.6	52.8	39.0	12.1	6.2
OR [95% CI]	1.08 [0.92; 1.28]		1.28 [0.48; 3.43]		1.87 [0.79;4.44]	
SMQ Ischaemic Heart Disease Broad including CPK non-specific of cardiac origin						
n (%)	347(9.1)	308(8.2)	17(9.8)	6(6.9)	25(4.3)	17(2.9)
Per 1000 PY	30.8	27.4	59.9	39.0	20.1	13.3
OR [95% CI]	1.13 [0.96; 1.33]		1.47 [0.56;3.88]		1.47 [0.78; 2.75]	
SMQ Ischaemic Cerebrovascular Conditions Narrow						
n (%)	184(4.8)	176(4.7)	3(1.7)	4(4.6)	5(0.9)	10(1.7)
Per 1000 PY	16.3	15.6	10.6	26.0	4.0	7.8
OR [95% CI]	1.04 [0.84; 1.28]					
SMQ Embolic & thrombotic events Narrow						
n (%)	306(8.0)	261(6.9)	8(4.6)	6(6.9)	11(1.9)	10(1.7)
Per 1000 PY	27.2	23.2	28.2	39.0	8.8	7.8
OR [95% CI]	1.18 [0.99; 1.40]					
SMQ Embolic & thrombotic events arterial Narrow						
n (%)	143(3.8)	132(3.5)	4(2.3)	6(6.9)	6(1.0)	3(0.5)
Per 1000 PY	12.7	11.7	14.1	39.0	4.8	2.3
OR [95% CI]	1.08 [0.85; 1.37]					
SMQ Embolic & thrombotic events venous Narrow						
n (%)	71(1.9)	47(1.2)	3(1.7)	0(0.0)	3(0.5)	1(0.2)
Per 1000 PY	6.3	4.2	10.6	0.0	2.4	0.8
OR [95% CI]	1.51 [1.04; 2.19]					
SMQ Cardiac arrhythmias Broad (excluding congenital and neonatal arrhythmias)						
n (%)	338(8.9)	330(8.8)	15(8.7)	5(5.7)	30(5.1)	27(4.7)
Per 1000 PY	30.0	29.3	52.8	32.5	24.1	21.0
OR [95% CI]	1.02 [0.87; 1.19]		1.56[0.55; 4.43]		1.10[0.64; 1.87]	

N: number of patients and number of Patient-Years (PY) by group
n(%) : number of patients with at least one emergent AE
Annual incidence per 1000 PY: number of patients with at least one AE per 1000 patients-year
OR[95%CI]: odds ratio and confidence interval (Mantel-Haenszel estimate for OSA 2011)

The PRAC noted that the SMQ data comparing strontium ranelate treated PMO women with placebo showed an increase in SMQ myocardial infarction narrow of 2.1 events per 1000 PY, OR 1.6 (1.07-2.38) and SMQ Ischaemic Heart disease broad 3.4 events per 1000 PY, 1.13 (0.96-1.33).

The increase in SMQ Embolic & thrombotic events was 4.0 events per 1000 PY, OR 1.18 (0.99-1.40). Especially the SMQ of Venous embolic and thromboembolic events the OR was higher in the strontium ranelate treated patients 2.1 events per 1000 PY, OR 1.51 (1.04-2.19).

In light of these numbers, the increased risk for myocardial infarction seems to be of a similar magnitude as the risk of venous thromboembolism associated with strontium ranelate treatment.

Findings from other study populations, male osteoporotic patients and osteoarthritis patients give some support for an increased cardiac risk of strontium ranelate. For instance, an increase of serious cardiac disorders compared to placebo of 12.7 events per 1000 PY in osteoporotic men and 8.2 events per 1000 PY in osteoarthritis patients was observed in strontium ranelate treated patients. The smaller numbers of patients make these observations more uncertain compared to the data in PMO women.

Cerebrovascular disease was not overrepresented in strontium ranelate treated patients talking against universal thrombotic potential of strontium ranelate. This finding is in line with the potential mechanistic considerations on calcium-like effects: calcium supplementation has been associated with none or non-significant increases in stroke in studies that found an association with myocardial infarctions and ischemic cardiac disease. Irrespectively, it is difficult to disregard the increase in serious cardiac disorders and MI data based on a lack of signal for cerebrovascular disease.

- **Cardiac arrhythmia**

In PMO women, the proportion of patients with cardiac arrhythmias (SMQ cardiac arrhythmia broad excluding congenital and neonatal arrhythmias) was similar in the strontium ranelate and the placebo group: 8.8% and 8.9% respectively, OR [95% CI] = 1.02[0.87; 1.19].
In osteoporotic men, the proportion of patients with cardiac arrhythmias was higher in the strontium ranelate group (8.7% versus 5.7%) but this can be explained by a higher proportion of patients with a medical history of arrhythmias (20.2% versus 11.5%).
In the osteoarthritis population, as in the PMO women, no difference versus placebo was observed (5.1% versus 4.7%).

- **Embolic and thrombotic events**

In PMO women, the risk of **venous thromboembolic** events with strontium ranelate are already considered as identified with a statistically significant increase in the incidence of VTE (SMQ embolic and thrombotic events venous narrow) in the strontium ranelate group versus placebo: 1.9% versus 1.2% respectively with an OR [95%CI] of 1.51 [1.04; 2.19]. Findings from the smaller studies in osteoporotic men and in osteoarthritis are in line with these results with an incidence of 1.7% versus none in men with osteoporosis and 0.5% versus 0.2% in osteoarthritis population.

Conversely, there is no increased risk of **arterial thrombotic** events with strontium ranelate as compared with placebo in PMO women (SMQ embolic and thrombotic events arterial narrow): 3.8% with strontium ranelate versus 3.5% with placebo, OR [95%CI] = 1.08[0.85; 1.37], in osteoarthritis (1.0% vs 0.5%) and in osteoporotic men (2.3% versus 6.9%).

- **Ischaemic cardiac events**

In the postmenopausal osteoporotic studies (OSA 2011 strontium ranelate 2g versus placebo), a significant increase in myocardial infarction (SMQ MI narrow) was observed in the strontium ranelate group compared to the placebo group (1.7% vs 1.1%, OR [95%CI] =1.6 [1.07; 2.38]). Regarding the risk of ischemic heart disease (SMQ IHD broad), no statistically significant difference was found between both groups (OR [95%CI] =1.13 [0.96; 1.33]). Similarly, no between groups difference was observed (OR [95%CI] =1.08[0.92; 1.28]) when non-specific CPK increase and/or abnormalities were excluded from the SMQ (possible confounding factor with strontium ranelate). Events from SMQ ischemic cerebrovascular condition narrow were equally reported in the strontium ranelate and in placebo group (OR [95%CI] =1.04 [0.84; 1.28].

In osteoporotic men, three patients (1.7%) in the strontium ranelate group versus one patient in the placebo group (1.1%) presented with an event myocardial infarction. The incidence of ischemic heart disease (SMQ IHD broad) was not statistically significantly higher in the strontium ranelate group as compared to the placebo group: 9.8% in the strontium ranelate group versus 6.9% in the placebo group (OR [95%CI] = 1.47 [0.56; 3.88]). The proportion of patient with an emergent ischemic cerebrovascular event (SMQ ischemic cerebrovascular condition narrow) was lower in the strontium ranelate group as compared to the placebo group: 1.7% versus 4.6%, respectively.

In osteoarthritic patients, 5 patients (0.9%) in the strontium ranelate group versus 1 patient (0.2%) in the placebo group presented with an event myocardial infarction. The incidence of ischaemic heart disease (SMQ IHD broad) was not statistically significantly higher in the strontium ranelate group as compared to the placebo group: 4.3% in the strontium ranelate group versus 2.9% in the placebo group (OR [95%CI] = 1.47 [0.78; 2.75]. Similarly, in this population, the frequency of ischaemic cerebrovascular events was lower in the strontium ranelate group as compared to the placebo group: 0.9% versus 1.7%, respectively.

Venous thromboembolic events

Regarding the venous thromboembolic events, in the PMO women, the risk of venous thromboembolic events with strontium ranelate is identified with a statistically significant increase in the incidence of VTE (SMQ embolic and thrombotic events venous narrow) in the strontium ranelate group versus placebo: 1.9 versus 1.2% respectively with an OR [95%CI] of 1.51 [1.04;2.19]. Findings from the smaller studies in osteoporotic men and in osteoarthritis are in line with an increased risk with 1.7% versus 0 in men with osteoporosis and 0.5 versus 0.2% in osteoarthritis population.

Regarding VTE, new contraindications for current or previous VTE, including deep vein thrombosis and pulmonary embolism as well as temporary or permanent immobilisation due to e.g. post-surgical recovery or prolonged bed rest were introduced following the referral under Article 20 of Regulation (EC) No 726/2004, finalised in March 2012. Those are intended to reduce the risk for VTE in the target population. The impact of these measures on reduction of risk is unclear. However, data recently evaluated within the ongoing type II variation for a new indication in osteoarthritis raise some concern. Despite that Medical history of VTE (including pulmonary embolism) or high risk of venous thromboembolism were exclusion criteria in the osteoarthritis study, there was a numerical increase in VTE: 5 events /548 for the 1 g SrRan group, 3 events /564 events for the 2 g SrRan group, compared with one event /556 in the placebo group.

Ischaemic cardiac events

Randomized studies

In PMO women, results showed statistically increase in SMQ myocardial infarction in PMO studies where 1.7% of patients experienced an event MI in the strontium ranelate group vs 1.1% in the placebo group, OR = 1.6 [1.07; 2.38]. This difference was driven by one study, TROPOS (n= 5029) among the seven studies performed in PMO versus placebo as detailed in Table 5.

Table 5 - Emergent MI (SMQ MI narrow) in the different studies constituting OSA PMO women

Studies*	Sample size S 129112gr/ placebo	Exposure [days(SE)] S 129112gr/ placebo	MI [n (%)] S 12911 2gr	MI [n (%)] Placebo
CL2-004	87/91	671.8 (202.1)/ 687.5 (192.5)	none	1 (0.6%)
CL2-005	56/57	620.5 (255.4)/ 599.3 (262.9	none	none
CL3-009 (SOTI)	826/814	1137.3 (519.8)/ 1137.4 (480.0)	6 (0.7%)	9 (1.1%)
CL3-010 (TROPOS)	2526/2503	1177.7 (702.5)/ 1189.9 (676.0)	58 (2.3%)	30 (1.2%)
CL3-013	67/65	351.1 (76.9)/ 348.4 (82.3)	none	none
CL3-015	164/165	360.2 (90.2)/ 360.9 (95.2)	none	none
CL3-017	77/74	340.2 (116.4)/ 353.3 (106.9)	none	none

**Details on the objective of the studies are presented in section 1.*

Some limitations are attached to this analysis: the main risk factors were not specifically taken into account in the study population randomization, cardiac events have not been adjudicated by a dedicated

committee, trials were not designed to accurately assess the cardiovascular safety, and events were reported by the investigators which may have limited their interpretation.
No major discrepancies in the cardiovascular risk factors at baseline were observed in the strontium ranelate group as compared to the placebo group.
The number of sudden deaths in PMO studies was lower in the strontium ranelate group. Importantly, the proportion of fatal MI was lower in the strontium ranelate group than in the placebo group (14.7% vs 23.3% of the MI were fatal, respectively) and no difference in the cardiovascular mortality was observed between the 2 groups.

The PRAC acknowledged that these studies were not designed to assess cardiovascular safety and that the cardiac events were non-adjudicated. However, myocardial infarction has well established criteria in clinical practice, in contrast to overall cardiac disorders which are clinically not as well-defined. Also symptoms of non-MI ischaemic heart disease may be diffuse in women and clinically challenging to diagnose. Consequently, the SMQ MI narrow data could be considered the most reliable of the cardiac data outcomes.

The seriousness and outcome of "myocardial infarction" in OSA 2011 and in Long term 2g are presented in the table below.

	OSA 2011		Long term 2 g
	S12911 2g	Placebo	
N	3803	3769	5819
n(%)	64 (1.7)	40 (1.1)	97 (1.7)
NEAE	68	43	105
Serious (%)	62 (91.2)	35 (81.4)	95 (90.5)
WEAE	20 (29.4)	13 (30.2)	29 (27.6)
Outcome			
Recovered	36 (52.9)	19 (44.2)	52 (49.5)
Improvement	14 (20.6)	11 (25.6)	19 (18.1)
Not recovered	8 (11.8)	3 (6.7)	14 (13.3)
Fatal	10 (14.7)	10 (23.3)	19 (18.1)
Unknown	0 (0.0)	0 (0.0)	1 (0.9)

Data are expressed as number of emergent events and corresponding percentage

WEAE= Withdrawal Emergent Adverse Event

Concerning the MI outcome in the study, proportion of "fatal MI" was lower in the strontium ranelate group as stated by the MAH whereas the proportion of "serious MI" and "not recovered from MI" was higher. The number of patients in different outcome categories is limited; categories and the follow up time for outcome are not clearly defined. Approximately 30% of the MI in both groups were withdrawal emergent adverse events.

According to the MAH, among the serious cardiac events or MI, 17.5 % of patients stopped the study treatment because of the event. No specific follow up was set up for these patients which mean that no mortality data after study discontinuation was included in the outcome cardiovascular death. Consequently, it is not considered possible to draw any firm conclusions on MI outcome differences between the groups.

In addition, no statistically significant difference in the risk of ischemic heart disease (SMQ IHD broad with or without including nonspecific CPK increase), in the risk of cerebrovascular events which could be linked to an arterial thrombosis and in the risk of arterial thrombotic events was found between the 2 groups
Emergent myocardial infarctions were reported regularly over time in each treatment group. Detailed results on time of onset are provided in Question 2.

In 2007, at the time of TROPOS study (5 years data) report submission a specific evaluation of coronary artery disorders and heart failure was performed. It was assessed by the CHMP and the FUM was fulfilled with no signals considered to raise further concerns: *"The MAH has submitted the requested analysis of cardiac safety for strontium ranelate. There are no signals that raise further concerns"*.

In March 2012, in the study supporting **male osteoporosis** registration (CL3-12911-032), a non-significant increase of ischemic heart disease related events (IHD) was observed (OR of 1.28[0.48; 3.43]. After adjustment on the medical history related to cardiac disorders which were unbalanced between the 2 groups (higher proportion of patients with medical history of ischemic heart disease, glucose metabolism disorders and arrhythmias in the strontium ranelate group, see details in part 2.2), HR for IHD broad was HR=1.06 [0.41-2.76].
Three (3) patients presented with a myocardial infarction in the strontium ranelate group versus 1 patient in the placebo group. More medical histories of IHD, diabetes, arrhythmias and hypertension were reported in the strontium ranelate group as compared to the placebo group.

Finally, in **osteoarthritis population**, a greater number of serious cardiac events (mainly ischaemic events) were observed in the strontium ranelate 2gr group than in the placebo group (2.7% vs 1.9% respectively) all occurring in patients with risk factors for ischemic events at baseline. This difference between groups might be explained by an unbalance in risk factors with in the strontium ranelate 2g group more patients over 65 years (44.9% vs 39.0% respectively), with hypertension (49.3% versus 46.6%), with at least one risk factor of ischemic cardiac event (78.7% versus 75.7%) and more patients' treated with coxibs at inclusion (7.4% versus 3.2%). Five (5) patients presented with a myocardial infarction in the strontium ranelate group versus 1 patient in the placebo group. All patients had at least one risk factor of ischemic cardiac event. No specific time pattern could be evidenced. There was no statistical increase in the risk to have an ischaemic cardiac event (SMQ IHD broad) OR=1.47, 95%CI[0.8;2.7].

Results of the cohort study in PMO women
An observational international prospective cohort survey (non-interventional) was performed in seven countries (France, Germany, Spain, United Kingdom, Austria, Italy, Netherlands) with the main objective to follow-up during 3 years a cohort of post-menopausal women treated with strontium ranelate with a special focus on all potential safety concerns.
The cohort consisted of 12,702 patients. Mean age was 69.0 years [±10.3] with 16.5% of patients being older than 80 years and 46.1% having at least one prevalent osteoporotic fracture.
Mean BMI was 25.6±4.3 kg/m², medical history of cardiac disorders was reported in 10% of patients, history of hypertension in 37.4% of patients and dyslipidaemia in 16.3% of patients. Ninety five (95) percent of patients had a follow-up with a mean follow up duration of 32 months and a mean treatment duration of 25.2 months (24 956 patient-years of treatment).

Cardiac events and particularly ischaemic heart disease were also investigated in this study (table below)

Table 6 - Cardiac events – incidence in the cohort study –Safety Set – N=12.076)

	Incidence
SOC cardiac disorders	
- n (%)	200 (1.7%)
- annual incidence (/1000 PY)	7.7
- serious adverse events (n(%))	159 (68.5%)
SMQ Ischaemic heart disease	
- n (%)	66 (0.6%)
- annual incidence (/1000 PY)	2.5
SMQ Myocardial infarction	
- n (%)	33 (0.3%)
- annual incidence (/1000 PY)	1.3
Sudden death and cardiac sudden deaths (n)	7

n = number of patients with at least one emergent AE in a given level; PY: annual incidence per 1000 patients-years

The annual incidence of myocardial infarction in the cohort study was 1.3 per 1000 -PY similar or lower to those observed in untreated women as mentioned in the Framingham heart study (incidence between 3.2 and 11/1000-PY) (Incidence and prevalence chart book on cardiovascular and lung disease, 2006).

The PRAC noted that the cohort had a low incidence of reported MI events (1.3 per 1000 PY) and did not show an increased incidence of MI in comparison to historical Framingham cohort incidence and prevalence chart book on cardiovascular and lung disease, 2006 (incidence between 3.2 and 11 per 1000 PY). However, the PRAC considered that the evidence quality from this type of comparisons is weak compared to large randomized placebo controlled trials and not enough to reject the hypothesis of an increased risk of MI associated with the treatment.

Post-marketing surveillance

Since the introduction of strontium ranelate on the market (September 2004), the cumulative number of events received for ischemic heart disease and myocardial infarction (until 20th February 2013) are as follows:

- A total of 48 events corresponding to the SMQ IHD broad excluding the increase in CPK non-specific of cardiac origin (of which 37 serious) have been reported in 41 patients for an estimated incidence of 1.2/ 100 000 PY.
- A total of 24 cases of events included in the SMQ myocardial infarction narrow were reported, among them only 16 cases corresponded to a myocardial infarction. 8 remaining cases due to troponin increased in a context of confirmed pulmonary embolism or diagnosis not confirmed by autopsy were excluded. The estimated incidence of MI is low: 0.5/100 000 patient-years. A risk factor or medical history was observed for 62.5% of the patients, mainly medical history of ischaemic heart disease (31.2%), hypertension (25.0%), dyslipidemia (25.0%) and diabetes (18.7%).
- 25 cases of death following cardiovascular events have been reported which corresponds to an incidence of 0.4/100 000 patient-years which is very low for the target population treated with Protelos/Osseor.

Details are presented in the two tables below.

Table 7 - All cases reported in Argus database included in SMQ "IHD " except CPK increase from Marketing Authorisation until 20-FEB-2013

ADR TERM	Cumulative number of events from MA to 20 Feb 2013	
	N (non- HCP)	S
Cardiac disorders		
Acute coronary syndrome	3 (0)	3
Acute myocardial infarction	4 (0)	4
Angina pectoris	9 (1)	5
Arteriosclerosis coronary artery	2 (1)	1
Coronary artery stenosis	2 (0)	2
Myocardial infarction	8 (4)	8
Myocardial ischaemia	1 (0)	1
Sub-total events	29 (6)	24
Sub total ICSR	29 (6)	24
Investigations		
Cardiac enzymes increased	2 (0)	1
Electrocardiogram ST segment depression	2 (0)	2
Electrocardiogram T wave inversion	5 (1)	4
Troponin increased	7 (0)	5
Troponin T increased	2 (0)	0
Sub-total events	18 (1)	12

Sub total ICSR	15 (1)	9*
Surgical and medical procedures		
Coronary arterial stent insertion	1 (0)	1
Sub-total events	1 (0)	1
Sub total ICSR	1 (0)	1
Total events	**48 (7)**	**37**
Total ICSR	**41 (7)**	**31**

N = Total number of terms; (non-HCP) = Number of non HCP cases among the total number of cases
S = Number of serious events among the total number of terms, Seriousness are evaluated at event level
**: Number of cases (by SOC) with at least one serious event within the SMQ Myocardial infarction*
HCP= HealthCare Professional

Table 8 - All cases reported in Argus database included in SMQ narrow "Myocardial infarction" - from Marketing Authorisation until 20-FEB-2013

ADR TERM	Cumulative number of events from MA to 20 Feb 2013	
	N (non- HCP)	**S**
Cardiac disorders		
Acute coronary syndrome	3 (0)	3
Acute myocardial infarction	4 (0)	4**
Myocardial infarction	8 (4)	8
Sub-total events	15 (4)	15
Sub total ICSR	15 (4)	15**
Investigations		
Troponin increased	7 (0)	5
Troponin T increased	2 (0)	0
Sub-total events	9 (0)	5
Sub total ICSR	9 (0)	5*
Total events	**24 (4)**	**20**
Total ICSR	**24 (4)**	**24**

N = Total number of terms; (non-HCP) = Number of non HCP cases among the total number of cases
S = Number of serious events among the total number of terms, Seriousness are evaluated at event level
**: Number of cases (by SOC) with at least one serious event within the SMQ Myocardial infarction*
*** in 1 case the diagnosis of AMI was not confirmed by the autopsy*
HCP= HealthCare Professional

No signal regarding cardiac events was detected in post marketing surveillance involving 3,402,769 patient-years of treatment and in the cohort study including more than 12,000 patients.

MI is not a labeled adverse event for strontium ranelate and occurs commonly in the elderly population. Moreover, the increased risk for MI is not closely time-related to the treatment start with strontium ranelate but constant over time. Therefore, the PRAC pointed out that it is unlikely that a MI occurring several months or years after treatment start with strontium ranelate in these elderly patients with multiple concomitant diseases is reported as an adverse event in signal detection databases. This might explain why no signal was observed for MI in post marketing surveillance in contrast to clinical studies.

A nested case-control study using the CPRD

To assess more accurately the risk of ischaemic cardiac events, in May 2012, the CHMP endorsed the proposal of the MAH to perform "*a specific study in osteoporotic patients to further assess the risk of ischaemic cardiac events, using the CPRD database. This observational retrospective study will use a population-based cohort to assess the risk of ischemic cardiac events, and a nested case-control study to investigate the potential association with strontium ranelate*."
The protocol was approved by the Independent Scientific Advisory Committee (ISAC) in July 2012.

Study design outlines

The study design consisted of a descriptive cohort approach with a new user design in men and women, and a case-control analysis nested in the cohort of osteoporosis (OP) treated women. The primary outcomes were first definite* myocardial infarction (MI), hospitalisation due to MI and cardiovascular death. These outcomes were identified using GP data as well as linked datasets (corresponding to hospitalizations HES data and ONS death data). A nested case-control analysis was performed for each of the three primary outcomes. Incident cases were matched to 6 to 10 controls per year of birth, calendar date and duration of prior osteoporosis treatment duration. In the main analyses, exposure to strontium ranelate (SrRan) and alendronate was defined as current if the last treatment episode of the considered treatment stopped less than a month before index date. Several sensitivity analyses were set up to deal with different scenarios of the main exposure of interest. Case-control analyses were based on a conditional logistic regression and adjusted for a large range of pre-defined risk and confounding factors**. Fully adjusted analyses were based on a backward selection of all factors significant in univariate analyses (20% threshold).

** The MI was qualified as definite if there was a MI record and the patient died within 30 days, or there was a relevant treatment initiation (statins, nitrates, beta-blockers, etc.) plus other supporting evidence of MI (such as location of infarct, coronary artery revascularization, raised cardiac enzymes, etc.), both within 2 months of the MI. Analyses on definite MI were also restricted to the first MI record, thus excluding patients with prior MI (more details in the protocol).*
*** Region, prior UTS follow-up, obesity, smoking status, small area socio-economic status (IMD), cardiovascular treatments per class (statins, fibrates, beta-blockers, calcium-channel blockers, drugs acting on renin-angiotensin system, diuretics, other anti-hypertensives, nitrates, anti-platelets), anti-diabetics, HRT, calcium and vitamin D supplementation, other anti-osteoporotics, previous MI (in case of recurrent MI).*

Patient's characteristics (cohorts)

As expected, the study population included a large majority of OP-treated patients (between 80 and 90% according to the cohort) and elderly patients (between 61% and 70% of them over 70 years old). Some differences in patients' profile were observed in the patients initiating strontium ranelate compared to the patients initiating alendronate. The proportion of men was smaller (10.1% *versus* 20.5%, respectively) and they were in average 3 years older (74.9 years *versus* 71.7 years, respectively). This reflects the fact that strontium ranelate was not indicated in men in the UK during the study period and is recommended as a third-line anti-osteoporotic treatment (NICE recommendations). Other consequences of these prescription particularities are that time since diagnosis was nearly twice longer in patients treated with strontium ranelate than in those treated with alendronate (42.4 months and 21.8 months, respectively) and that strontium ranelate was the first anti-osteoporotic treatment in only one third of patients (33.6%) in the strontium ranelate cohort, whereas alendronate was commonly the first treatment in the alendronate cohort (87.7%). In addition, the mean exposure to strontium ranelate was about twice shorter compared to the mean exposure to alendronate (7.6 months *versus* 14.6 months, respectively).

Results on first definite MI (nested case-control)

Table 9 - Association of SrRan / alendronate with first definite MI in CPRD – Main analyses

	Main analysis (1) (threshold=1 month)	
	Adjusted OR	[95% CI]
SrRan (current vs never)	1.05	[0.68;1.61]
Alendronate (current vs never)	0.98	[0.83;1.15]
SrRan vs alendronate (current)	1.13	[0.74;1.73]

(1) Current exposure = ongoing at index date or ending less than 1 month before

Results on MI with hospitalization (nested case-control)

Table 10 - Association of SrRan / alendronate with MI with hospitalisation in CPRD - Main analyses

	Main analysis (1) (threshold=1 month)	
	Adjusted OR	[95% CI]
SrRan (current vs never)	0.84	[0.54;1.30]
Alendronate (current vs never)	0.85	[0.73;0.99]
SrRan vs alendronate (current)	1.12	[0.72;1.74]

(1) Current exposure = ongoing at index date or ending less than 1 month before

Results on cardiovascular death (nested case-control)

Table 11 - Association of SrRan / alendronate with cardiovascular death in CPRD – Main analyses

	Main analysis (1) (threshold=1 month)	
	Adjusted OR	[95% CI]
SrRan (current vs never)	0.96	[0.76;1.21]
Alendronate (current vs never)	0.80	[0.72;0.88]
SrRan vs alendronate (current)	1.27	[1.00;1.61]

(1) Current exposure = ongoing at index date or ending less than 1 month before

As a matter of fact, the comparison of strontium ranelate and alendronate led to a borderline significant association for cardiovascular death (OR=1.27, 95%CI [1.00;1.61]), driven by the observed decreased rate under alendronate.

All sensitivity analyses showed consistent results with the main analyses.

Rationale of the study design

In recent years, numerous drug safety studies using CPRD data with a nested case-control design have been carried out, with examples for bisphophonates or cardiovascular outcomes (Vinogradova 2013, Varas-Lorenzo C, 2007).
In this study, the case-control approach was nested in a cohort of patients who were all treated for osteoporosis, with the aim to reduce the potential heterogeneity between patients. A nested case-control study was also chosen for the following advantages if offers: it allows for a good control of confounding variables, as well as better quantification of time-dependent exposures clinically relevant through potentially not too complex analyses (Essebag 2003, Etminan 2004).
This design allows for control of potential confounding through matching. In this study, age, calendar time and disease duration were the main confounding factors (i.e. associated with both the outcome and the exposure of interest). Strontium ranelate is still a recently marketed treatment and recommended as third-line while alendronate is a long marketed first-line treatment. For this reason, cases and controls were matched on year of birth, calendar date and prior osteoporosis treatment duration +/-1 year (i.e. time since first prescription of any anti-osteoporotic treatment, proxy for disease severity). Age was used as an exact matching criteria, as previously recommended by two scientific advisors of this study (de Vries 2006). Moreover, a nested case-control approach has also superior computational efficiency than a cohort approach when studying multiple time-dependent exposures as exposure of interest or potential confounders. The exposure to strontium ranelate and alendronate was examined at different time intervals before the index date and challenged through different sensitivity analyses (de Vries 2006).
Besides, there was a need to consider cardiovascular treatments among potential confounders and adjustment factors in addition to strontium ranelate and alendronate exposure.

In the cohort approach, patients' profile at treatment initiation showed that, as expected, patients prescribed strontium ranelate or alendronate were different in terms of age (74.9 years versus 71.7 years respectively) and osteoporosis severity (42.4 months and 21.8 months for time since diagnosis respectively, and 33.6% and 87.7% of strontium ranelate and alendronate respectively received the treatment as first-line). This unavoidable heterogeneity between patients driven by the treatment recommendations leads to a channelling bias that is very challenging to overcome. Even if the case-control approach allows to better handle the heterogeneity of patients (by matching cases and controls on the most important confounders and by adjusting analyses on the remaining risk and confounding factors), residual unmeasured confounding cannot be excluded, in particular in this study where studied treatments have different recommendations of use. As a consequence, results of comparisons between strontium ranelate and alendronate should be interpreted cautiously.

Conclusion

The complete final study report will be submitted in May 2013 and consequently a full study assessment is not possible at this time. The main results indicate that compared to osteoporosis patients without a specific anti-osteoporotic treatment, there was no increased risk associated with strontium ranelate treatment.

Compared to current alendronate users, however, the strontium ranelate users had a numerically higher odds ratio for MI, MI with hospitalization and borderline significant higher risk for cardiovascular death OR 1.27 (1.00-1.61).

Mechanistic considerations

Two hypotheses were explored further:

1. The role of a potential calcium like effect of strontium on cardiac events although the relationship between calcium and ischemic cardiac events remains unclear.

Some observational studies have suggested that dietary calcium intake or moderate calcium supplementation might protect against cardiovascular diseases (Wang 2012) whereas other found that calcium supplementation above 1400 mg/day were associated with an increased risk of death rates from all causes, cardiovascular diseases, ischemic heart disease but not from stroke (Michaelsson 2013). A recent meta-analysis conducted in 11 eligible trials (11921 subjects, who received a dose of calcium of at least 1000 mg daily, median follow up 4 years) found 27-31% significant increase in risk of myocardial infarction, 12-20% non-significant increase in risk of stroke and without effects on mortality (Reid 2011).

2. A possible effect of strontium on hemostasis

In vitro and animal studies did not show any effect of strontium ranelate on coagulation parameters. In particular there were neither anti-aggregating nor pro-aggregating effects of strontium ranelate on platelets and no effect on thrombin formation in vitro.

Haemostasis parameters in clinical trials:

A 3-month phase I study (CL1-12911-014 FRA) was conducted in healthy postmenopausal volunteer females whose age ranged from 60 to 81 years. Prothrombin Time (PT), Quick time, fibrinogen, antithrombin III, protein C, protein S, activated protein C resistance, Plasminogen Activator Inhibitor (PAI), prothrombin fragment 1 + 2, D-Dimers and factor VIII were studied.

The only change was a moderate increase of the Factor VIII level occurred in the S 12911 group as compared to the placebo group the estimated difference in relative change between group was 12.27 with a 95%CI of [3.46 ; 21.08]%). When considering individual participants changes using a clinically relevant threshold as defined in the protocol value > 200% which was considered as a potentially clinically significant abnormal value, no case was reported in Protelos groupe neither in placebo group.

In the CL3- 12911- 032 study in men with osteoporosis, haemostasis parameters were assessed in all patients at inclusion and in a subgroup of patients at the following visits. The number of patients with PCSA values for the different parameters were sparse and similar in both groups.

In the CL3-12911-018 study (osteoarthritis indication), a blood sampling for a haemostasis evaluation was collected for all included patients at inclusion visit and at all the following visits for all patients. The number of patients experiencing at least one emergent potentially clinically relevant abnormal value was small and similar in both the SrRan 2g and the placebo groups except for factor VIII (i.e >200) with 40 patients out of 564 (8.5%) in the strontium ranelate group and 14 out of 556 (3.0%) in the placebo group.

Literature data:

Regarding factor VIII, several epidemiological studies have suggested that increased Factor VIII levels could be associated with athero-thrombotic events. (Cortellano, 1992, Bank 2004, Kucharska-Newton 2009, Russel 1999, Tanis 2006), but interpretation of these data is somewhat difficult: a) the definitions of the outcome events differ according to the study; b) confounding factors, especially the inflammatory response, were not well controlled. In addition, high variation of Factor VIII activity has been shown among subjects (Bach 2010; Campos 2011). Finally, only few studies have evaluated the effects of Factor VIII elevation on arterial thrombosis in animal models with conflicting results.

The PRAC was of the view that, given the thrombotic potential of strontium ranelate, there is a possible mechanistic rationale for a wider cardiovascular risk. Strontium ranelate treatment was associated with moderate increased levels of factor VIII in healthy postmenopausal females and with clinically significant elevations (>200%) in osteoarthritis patients (8.5% in SrRan 2g vs. 3.0% in placebo). Epidemiological studies have suggested that increased Factor VIII levels could be associated with athero-thrombotic events.

There are conflicting published results on the relationship between calcium and ischemic cardiac events. A recent meta-analysis of 11 trials (11,921 subjects) found an increase in myocardial infarction in patients receiving daily calcium. Strontium could theoretically have a similar calcium-like effect on cardiac events.

PRAC Question 2: In addition, it is also of importance to evaluate when the events occur in relation to treatment start. Such data should be presented.

In response to this question, the MAH presented the following data:

Table 9 - Cumulative incidence of MI in PMO women

			S12911 2g	Placebo
	Npat (*)	N	64	40
[0-6] months	Patients at risk	N	3803	3769
	Events	N	7	6
	Incidence	E(SE) (1)	0.19% (0.07%)	0.16% (0.07%)
]6-12] months	Patients at risk	N	3296	3354
	Events	N	9	4
	Incidence	E(SE) (1)	0.48% (0.12%)	0.29% (0.09%)
]12-18] months	Patients at risk	N	3049	3114
	Events	N	6	3
	Incidence	E(SE) (1)	0.66% (0.14%)	0.39% (0.11%)
]18-24] months	Patients at risk	N	2606	2660
	Events	N	6	5
	Incidence	E(SE) (1)	0.90% (0.17%)	0.59% (0.14%)
]24-30] months	Patients at risk	N	2444	2500
	Events	N	7	8
	Incidence	E(SE) (1)	1.21% (0.21%)	0.93% (0.18%)
]30-36] months	Patients at risk	N	2178	2213
	Events	N	5	4
	Incidence	E(SE) (1)	1.45% (0.23%)	1.12% (0.21%)
]36-42] months	Patients at risk	N	2041	2038
	Events	N	7	3
	Incidence	E(SE) (1)	1.80% (0.27%)	1.28% (0.23%)
]42-48] months	Patients at risk	N	1836	1824
	Events	N	5	2
	Incidence	E(SE) (1)	2.08% (0.30%)	1.39% (0.24%)
]48-54] months	Patients at risk	N	1669	1437
	Events	N	7	2
	Incidence	E(SE) (1)	2.63% (0.36%)	1.56% (0.27%)
]54-60] months	Patients at risk	N	1100	1061
	Events	N	4	3
	Incidence	E(SE) (1)	3.02% (0.41%)	1.85% (0.32%)
]60-66] months	Patients at risk	N	958	805
	Events	N	2	
	Incidence	E(SE) (1)	3.40% (0.50%)	

Npat (*): number of patients with an emergent AE from the SMQ MI narrow

From these cumulative incidences, it can be concluded that the risk seems to remain constant overtime.

PRAC Question 3: The MAH should also discuss further need for risk minimization measures, and how this should affect the RMP.

In response to this question, the MAH proposed to reflect the information about the risk of myocardial infarction in the SmPC, as follows:

Section 4.8 Undesirable effects

Cardiac Ischemic Events
"In pooled placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase of myocardial infarction has been observed in Protelos treated patients (comparison based on patient years) compared to placebo (OR 1.6 (1.07-2.38), with no difference in overall cardiovascular mortality. This increase of myocardial infarction was not observed in a nested case control study nor during post marketing surveillance, including a large cohort study involving more than 12,000 patients."

In addition, the MAH proposed to update the Protelos RMP with additional measures in order to further explore the risk of myocardial infarction:

- Adjudication of cardiac events in ongoing Protelos clinical trials including the prospective cohort of osteoporotic men;
- Search for additional European epidemiological databases in countries where Protelos is more extensively used in first line treatment allowing a complementary comparison versus other antiosteoporotic drugs.

Furthermore, the MAH proposed to strengthen the pharmacovigilance procedures with monthly signal detection.

The PRAC considered insufficient the proposal of the MAH to add a wording in section 4.8 of the SmPC. The PRAC considered reasonable to try to reduce the target population by excluding patients with risk for ischemic cardiac disorders. This could also be supported by an argument put forward by the MAH that the increased MI risk was mainly due to results from the TROPOS study, which included patients at higher age and higher rate of cardiac co-morbidities. However, it should be remembered that the risk profile is partly overlapping for ischemic cardiac disorder and for osteoporosis.

PRAC Question 4: The number of fractures from the efficacy data (both vertebral and non-vertebral) should be summarized and presented for all clinical trials in postmenopausal osteoporosis, OSA population and osteoporotic men.

The OSA of post-menopausal women population includes 7 double-blind studies comparing strontium ranelate 2g to placebo:

2 phase II studies STRATOS/CL2-004 (Meunier, 2002; NP07869) and PREVOS/CL2-005 (Reginster 2002; NP08511),

2 pivotal phase III studies SOTI/CL3-009 (Meunier, 2004; NP08338/NP22819) and TROPOS/CL3-010 (Reginster 2005; NP08340/NP22824),

3 Asian phase III studies CL3-013 (Hwang 2008; NP22514), CL3-015 (Liu 2009; NP25026), CL3-017 (NP24357).

Fractures data are available from X-rays assessments of vertebral fractures (using a semi-quantitative method) for all studies except PREVOS where vertebral fractures are available from the reporting of adverse events. Non-vertebral fractures are assessed as efficacy measurements in SOTI and TROPOS studies and as reporting of adverse events in the five other studies.

As requested by the CHMP, all the fractures data, from all PMO women studies, whatever their data collection origin, are synthetized in the following table:

Table 10 - PMO women Phase II-III studies

	S12911 2g	Placebo
New vertebral fracture		
N	2924[(1)]	2945[(1)]
PY	9782.2	9852.6
n (%)	508 (17.4)	663 (22.5)
Per 1000 PY	51.9	67.3
OR [95% CI]	0.724 [0.636 ; 0.823]	
p-value	**p <0.0001**	
Non vertebral fractures		
N	3748[(2)]	3711[(2)]
PY	12621.6	12642.7
n (%)	426 (11.4)	492 (13.3)
Per 1000 PY	33.8	38.9
OR [95% CI]	0.839 [0.731 ; 0.964]	
p-value	**p = 0.013**	
Major osteoporosis-related peripheral fracture		
N	3748[(2)]	3711[(2)]
PY	12621.6	12642.7
n (%)	327 (8.7)	391 (10.5)
Per 1000 PY	25.9	30.9
OR [95% CI]	0.812 [0.696 ; 0.947]	
p-value	**p = 0.008**	
Hip fracture		
N	3748[(2)]	3711[(2)]
PY	12621.6	12642.7
n (%)	109 (2.9)	114 (3.1)
Per 1000 PY	8.6	9.0
OR [95% CI]	0.945 [0.724 ; 1.234]	
p-value	**p = 0.678**	
Wrist fracture		
N	3748[(2)]	3710[(2)]
PY	12621.6	12639.0
n (%)	112 (3.0)	125 (3.4)
Per 1000 PY	8.9	9.9
OR [95% CI]	0.883 [0.682 ; 1.145]	

p-value	**p = 0.348**	

Pelvic-sacrum fracture		
N	3748[(2)]	3710[(2)]
PY	12621.6	12639.0
n (%)	34 (0.9)	54 (1.5)
Per 1000 PY	2.7	4.3
OR [95% CI]	0.620 [0.403 ; 0.954]	
p-value	**p = 0.028**	

Ribs-sternum fracture		
N	3748[(2)]	3710[(2)]
PY	12621.6	12639.0
n (%)	61 (1.6)	90 (2.4)
Per 1000 PY	4.8	7.1
OR [95% CI]	0.665 [0.479 ; 0.924]	
p-value	**p = 0.014**	

Clavicle fracture		
N	3748[(2)]	3710[(2)]
PY	12621.6	12639.0
n (%)	7 (0.2)	10 (0.3)
Per 1000 PY	0.6	0.8
OR [95% CI]	0.692 [0.263 ; 1.821]	
p-value	**p = 0.454**	

Humerus fracture		
N	3748[(2)]	3710[(2)]
PY	12621.6	12639.0
n (%)	36 (1.0)	52 (1.4)
Per 1000 PY	2.9	4.1
OR [95% CI]	0.682 [0.445 ; 1.046]	
p-value	**p = 0.078**	

N: number of patients and number of Patient-Years (PY)
n (%) : number of patients with at least one event and %=(n/N)x100
Annual incidence per 1000 PY: number of patients with at least one event per 1000 patients-year
OR [95%CI]: odds ratio and confidence interval (naïve pooling)
p-value: Chi-square test

The PRAC noted that the extent of exposure in patient years differs from the extent in the main analyses of cardiac events in the OSA 2011 population. This is explained by the fact that the efficacy analyses were carried out considering all information about peripheral fractures occurrence up to 6 months after last treatment intake. However, the inclusion of this additional time period is not considered to overestimate the benefit of strontium ranelate, as the effect if anything would be reduced by stopping treatment. As the efficacy and safety results were presented by the MAH as incidences expressed per 1000-PY, comparisons of fractures and cardiac events can thus still be considered relevant for assessing the benefit / risk balance.

The reduction of non-vertebral fractures in strontium ranelate treated patients compared to placebo was 5.1 events per 1000 PY, OR 0.84 (0.73-0.96) and new vertebral fracture 15.4 events per 1000 PY, OR 0.72 (0.64-0.82). The reduction in non-vertebral fractures consisted mainly of fractures in ribs-

sternum 2.3 events, pelvic-sacrum 1.6 events and humerus 1.2 events per 1000 PY. There was no obvious difference between strontium and placebo treated patients in hip fractures in this population.

Main results from the individual studies

During the development program, the anti-fracture efficacy of strontium ranelate (Protelos/Osseor) was assessed in two placebo-controlled 5-year studies in post-menopausal osteoporotic women (PMO), SOTI and TROPOS, with main analyses performed at 3 years. These pivotal studies aimed at assessing the efficacy in reducing vertebral fractures (SOTI: 1649 PMO women with mean age 70 years) and non-vertebral fractures (TROPOS: 5091 PMO women with mean age 77 years). The primary endpoint of the other double-blind studies comparing strontium ranelate 2g to placebo included in the OSA population of post-menopausal women was the change in Bone Mineral density, they were not powered to evaluate the incidence of fractures as main endpoint. However, a few data are available in post-menopausal women either from X-rays assessments or from the reporting of fractures as adverse events.

Main results on the incidence of **vertebral fractures** in SOTI and TROPOS are summarized in the tables below.

Table 11 - Incidence over time of patients experiencing a new vertebral fracture over 3 years in SOTI and TROPOS

		Strontium Ranelate 2g	Placebo	Relative Risk [95% CI]	p value
SOTI	N	719	723		
n		139	222	0.59	**<0.001**
Incidence % (SE) [1]		20.9 (1.6)	32.8 (1.8)	[0.48; 0.73]	
TROPOS	N	1817	1823		
n		202	321	0.61	**< 0.001**
Incidence % (SE) [1]		12.5 (0.8)	20.0 (1.0)	[0.51; 0.73]	

Table 15 - TROPOS - Incidence over time of patients with at least one incident osteoporosis-related non-vertebral fracture* or one incident major osteoporosis-related peripheral fracture over 3 and 5 years- FAS**

		Strontium Ranelate 2g	Placebo	Relative Risk [2] [95% CI]	p value [3]
TROPOS	N	2479	2453		
Non-vertebral fractures					
Over 3 years					
n		233	276	0.84	**0.043**
Incidence % (SE) [1]		11.2 (0.73)	12.9 (0.77)	[0.71; 1.00]	
Over 5 years					
n		312	359	0.85	**0.032**
Incidence % (SE) [1]		18.6 (1.00)	20.9 (1.03)	[0.73 ; 0.99]	

Major osteoporosis-related peripheral fracture				
Over 3 years				
	n	181	225	0.81	**0.031**
	Incidence % (SE) (1)	8.7 (0.65)	10.4 (0.70)	[0.66; 0.98]	
Over 5 years				
	n	246	291	0.82	**0.025**
	Incidence % (SE) (1)	14.7 (0.92)	16.9 (0.95)	[0.69 ; 0.98]	

N: Number of patients in each treatment group
n : Number of patients with at least one incident osteoporosis-related peripheral fracture over each period
1: Estimated incidence (standard error)using Kaplan-Meïer method at selected time points
2: Estimate and 95% CI of the adjusted relative risk as compared to placebo;
3: Adjusted Cox model

In the MALEO study in osteoporotic men, only the incidence of symptomatic fractures, reported as adverse events, was described at M12. After 2 years of treatment, the incidence of non-clinical vertebral fractures was assessed as in PMO studies by a central X-ray reading centre.

The incidence of fractures observed during the period M0-M24 in the Safety Set is displayed in table (2.2.1) 1.

Table 16 - Occurrence of non-vertebral fractures – Safety set (M0-M24).

	Strontium ranelate 2g n=173	**Placebo n=87**
Hip fracture	1 (0.6%)	-
Great trochanter fracture	2 (1.2%)	
Pertrochanteric fracture	1 (0.6%)	
Rib fracture	-	1(1.1%)
Acetabulum fracture	-	1(1.1%)
Hand fracture	1(0.6%)	1(1.1%)
Foot fracture	1(0.6%)	1(1.1%)
ALL	**6 (3.5%)**	**4 (4.6%)**

Table 17 - Incidence of vertebral fractures in the Safety Set (M0-M24)

		Strontium ranelate 2g (N = 120)	**Placebo (N = 64)**	**All (N = 184)**
M0-M24				
Number of patient with new vertebral fractures	n (%)	7 (5.8)	5 (7.8)	12 (6.5)

N: Number of patient with a baseline and a post baseline assessable X-ray
n: Number of patients with a new of vertebral fracture
%: [n/N] x 100

The PRAC observed that, overall; the number of clinical and non-clinical fractures was low in the male population. In the male population treated with strontium ranelate, the absolute increase in serious cardiovascular adverse events was 1.36% compared to the absolute risk reduction in non-vertebral fracture 1.1%.

PRAC Question 5: Based on the issues requested above, the MAH should discuss the benefit/risk balance of strontium in the approved indications.

The MAH presented the table below showing the efficacy of strontium ranelate compared to other anti-osteoporotic drugs and place in the therapeutic landscape:

Table 12 - Efficacy of anti-osteoporotic treatments on the relative risk and absolute risk reduction of vertebral, non-vertebral and hip fracture occurrence over 3 years

Product	Study	Results		
		Vertebral Fracture Risk	Non-vertebral Fracture Risk	Hip Fracture Risk
Alendronate	FIT(1)	RR 0.53 ARR 7% p<0.001 95%CI [0.41-0.68] N=1946	NS	RR 0.49 ARR 1.1% - 95%CI [0.23-0.99]
Risedronate	VERT-NA(2)	RR 0.59 ARR 5% P=0.003 95%CI [0.43-0.82] N=1374	RR 0.6 ARR 3.2% p=0.02 95%CI [0.39-0.94] N=1627	
	HIP(3)			RR 0.7 ARR 1.1% p=0.02 95%CI [0.6-0.9] N=9331
Ibandronate	BONE(4)	RR 0.38 ARR - p=0.0001 95%CI [0.41-0.75] N=1952	**RR 0.31 ARR p= 0.01? -	-
Zoledronic acid	HORIZON(5)	RR 0.30 ARR 7.6% p<0.001 95%CI [0.24-0.38] N=5675	RR 0.75 ARR 2.7% p<0.001 95%CI [0.64-0.87] N=5675	RR 0.59 ARR 1.1% p=0.002 95%CI [0.42-0.83] N=5675
Raloxifene	MORE (6)	RR 0.5 ARR 10.5% - 95%CI [0.4-0.7] N=1535	NS	NS
Denosumab	FREEDOM(7)	RR 0.32 ARR 4.9% p<0.001 95%CI [0.26-0.41] N=7393	RR 0.80 ARR 1.5% p=0.01 95%CI [0.67-.095] N=7393	RR 0.60 ARR 0.5% p=0.04 95%CI [0.37-0.97] N=7393
Teriparatide	Neer et al 2001(8)	RR 0.35 ARR 9% p≤0.001 95%CI [0.22-0.55] N=892	RR 0.65 ARR 4% P=0.04 - N=1085	NS
Strontium ranelate	SOTI	RR 0.59 ARR 11.9% p<0.001 95%CI [0.48-0.73] N=1442		
	TROPOS		RR 0.84 ARR 1.7% p=0.04 95%CI [0.70-0.99] N=4932	***RR 0.64 ARR 2.1% p=0.046 95%CI [0.41-0.99

(1) Black DM, Cummings SR, Karpf DB et al. Lancet 1996; 348:1535-1541.
(2) Harris ST, Watts NB, Genant HK et al. JAMA 1999; 282:1344-1352.
(3) Mac Clung MR, Geusens P, Miller PD et al. N Engl J Med 2001; 344:333-340.
(4) Chesnut CH, Skag A, Christiansen C et al. J Bone Miner Res 2004; 19:1241-1249.
(5) Black DM, Delmas PD, Eastell R et al. N Engl J Med 2007; 356:1809-1822.
(6) Ettinger B, Black DM, Mitlak BH et al. JAMA 1999; 282:637-645.
(7) Cummings SR; San Martin J, Mac Clung MR et al. N Engl J Med 2009; 361:756-765.
(8) Neer RM, Arnaud CD, Zanchetta JR et al. N Engl J Med 2001; 344:1434-1441.
** treatment duration is 24 months; ARR: absolute risk reduction; ** in a subgroup with low femoral neck BMD T-score<-3 and with oral daily treatment; *** in a subgroup with high risk*

The safety profile of other anti-osteoporotic treatments are:

Biphosphonates: common acute adverse events with bisphosphonates for osteoporosis are gastrointestinal discomfort and acute influenza-like illness. Oesophageal reactions (oesophageal ulcers

and oesophageal erosions and oesophagitis) have been reported with the use of alendronate. A special warning is mentioned in Section 4 of the SmPC. Biphosphonates therapy has been associated with a risk of osteonecrosis of the jaw and atypical femoral fractures.

SERMs: Hot flushes and peripheral edema are known to be associated with raloxifene use. A meta-analysis to evaluate the effect of raloxifene on the risk of deep vein thrombosis and pulmonary embolism showed that therapy with raloxifene was associated with a 62% increase in the odds (odds ratio 1.62, $p < 0.001$) (Adomaityte 2008). Raloxifene is contra-indicated in patients with active or past history of VTE, in patients with severe renal impairment or with hepatic impairment.

Denosumab is a human monoclonal antibody that inhibits RANKL. The safety concerns may include infections, eczema and non-dermatologic reactions. Other safety issues may be attributed to an over-suppression of bone remodelling: hypocalcemia, decreased or delayed fracture healing, atypical fractures and osteonecrosis of the jaw.

Teriparatide: adverse effects may include orthostatic hypotension, transient hypercalcemia, arthralgia, and leg cramps. Increased risk of osteosarcoma is seen in rats exposed to high doses. Consequently, teriparatide is contraindicated in patients with risk of osteosarcoma, such as those with Paget disease, previous skeletal radiation, or unexplained elevation of alkaline phosphatase level.

The MAH stated that strontium ranelate treatment over 3 years is as effective as bisphosphonates, which are considered to be most efficient, in term of RRR and slightly better in terms of ARR. According to the MAH, this is true whatever the type of fractures (vertebral, non-vertebral and hip).

According to the MAH, regarding long-term efficacy, Protelos/Osseor is the only anti-osteoporotic treatment for which anti-fracture efficacy has been demonstrated over the long term (5 years) on both vertebral-, non-vertebral and hip fractures, with maintenance of this efficacy over the very long term (10 years) at both the vertebral- and non-vertebral levels.

The PRAC noted that a reduction in hip fractures was shown in a post-hoc analysis of a subgroup in the TROPOS study.

In comparison with other specific anti-osteoporotic treatments (bisphosphonates raloxifene, denosumab and teriparatide), the absolute and relative risk reductions of fractures in the corresponding pivotal studies are in the same range with strontium ranelate treatment. Comparisons of these treatments based on different studies should be made with caution as the reported fracture risk reductions are greatly influenced by the baseline risks in the studied populations and other confounders, for example calcium and vitamin D supplementation.

In addition, the PRAC noted that there have been 3 randomized controlled studies directly comparing strontium ranelate with alendronate (CL3-12911-019, CL3-12911-025, CL3-12911-030, data received from the MAH during procedure FUM 021.1). These studies were not designed and dimensioned to compare the anti-fracture efficacy. Consequently, the number of clinical fractures in the studies was few but numerically in favor of alendronate.

All	Str Ran 2g	Alendronate
N (PY)	392	269
Number of fractures	18 (4.6)	8 (3.9)
Annual incidence per 1000 PY	37.7	22.5

The MAH argued that while other anti-osteoporotic treatments reduce fractures either by decreasing bone resorption (bisphosphonates, ralixofen, denosumab) or by increasing bone formation (teriparatide), strontium ranelate has a more physiological mode of action, preserving bone metabolism without over-suppression of bone turnover. Other antiosteoporotic treatments have different but also important risks that might be related to their mechanism of action. For example, atypical fragility fractures and osteonecrosis of the jaw that have been reported with bisphosphonates could be linked to reduction of bone remodeling.

The PRAC acknowledged that strontium ranelate has a mode of action and a safety profile that is different from the other specific anti-osteoporosis treatments. The PRAC also noted that strontium ranelate is currently recommended as first line treatment in some European countries but as a third line treatment in others, whilst it is not approved in the USA.

4.2. Oral Explanation:

Following the assessment of the Request for Supplementary Information, the MAH was requested to present the following points in an oral explanation to the PRAC that took place on 8 April 2013:

- The benefit/risk balance in the current indications
- Given the MI risk identified, discuss adequate risk minimization measures.
- Discuss the possibility to define a sub population of osteoporosis patients where the benefit-risk balance would be favorable i.e. higher estimates of fracture prevention in comparison to the identified risks, including cardiac and vascular safety risks. This should include a discussion both from an efficacy and an overall safety perspective.
- The MAH should discuss the baseline characteristics of the treatment groups in the TROPOS trial to identify whether or not these findings may be explained by bias.

In the oral explanation the MAH pointed out that an increase in non-fatal MI in PMO women was only seen in randomised clinical trials. There is no conclusive evidence for mechanism behind increase risk of MI.

The MAH clarified that there was no imbalance in cardiovascular risk factors, at baseline between strontium ranelate and placebo groups in the TROPOS study.

During the oral explanation, the MAH presented new, retrospective analyses to try to identify a high risk population for MI in order to select a sub-population with a more favorable benefit/risk balance:

Analyses were performed on the pooled PMO studies (OSA 2011) to look for of significant interaction between baseline characteristics and treatment on occurrence of MI. Significant interaction with DBP > 90 mmHg was found. No interactions with other risk factors: age, BMI>25, diabetes, dyslipidemia or smoking habit were found.

The MAH defined a subgroup without history of IHD, nor DBP > 90 mmHg, nor SBP > 160 mmHg. In this subgroup, the MAH argued that there was no increased risk of MI in strontium ranelate treated patients and that the efficacy of fracture prevention was maintained in this group.

The MAH proposed following adjustment of the SmPC:

Section 4.4 Warning: *In pooled placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase of myocardial infarction has been observed in Protelos treated patients compared to placebo (OR 1.6 (1.07-2.38), with no difference in overall cardiovascular mortality. This increase of myocardial infarction was not observed in a nested case-control study nor during post marketing surveillance, including a large cohort study involving more than 12,000 patients* ***(see 4.8).***

Protelos is thus not recommended for female and male patients with history of ischemic disease including myocardial infarction. Protelos should not be initiated in patients with uncontrolled blood pressure.

The MAH proposed the following action plan:

1. Submission of study reports within the requested timelines:

–The report with the safety and efficacy in this subgroup population

–Nested case-control study report

2. Monitoring of the new proposed minimization measures:

–Non-interventional Safety Study to assess the effectiveness of the applied risk minimisation measures, including a description of the treated patient population in everyday clinical practice. First results will be submitted the end 2013 and then every year.

–Revised cohort study in male, to add female patients and control group (non treated Protelos group) with adjudication process for major CV events (prospective PASS study). Protocol ready for submission within 2 months

The PRAC was of the view that the retrospective analyses to identify a subgroup with lower risk have methodological weaknesses. There is uncertainty whether the proposed measures will reduce the risk to an acceptable level. Thus, the proposed risk minimization measures by the SmPC proposal are not considered sufficient. See discussion on the benefit-risk assessment below.

5. Benefit evaluation

Important Baseline Efficacy and Effectiveness Information

Strontium ranelate has been authorised for the treatment of osteoporosis in post-menopausal women to reduce the risk of vertebral, non-vertebral and hip fractures. The Marketing Authorization was granted by the European Commission on 21 September 2004. Vertebral fractures are reduced in osteoporotic women with at least one prevalent vertebral fracture (by 41% and 33% over 3 and 4 years respectively).

Non-vertebral fracture with relative risk reductions of 16% and 15% over 3 and 5 years, respectively, in particular at the hip (by 36% and 43% over 3 and 5 years respectively) in osteoporotic patients aged 74 years old or over (with a low BMD femoral and/or lumbar Tscore ≤-2.4).

Newly Identified information on Efficacy and Effectiveness

The European Commission granted marketing authorization for strontium ranelate for the treatment of osteoporosis in men at increased risk of fracture on 27 June 2012. The approval was based on an

international, unbalanced (2:1), double-blind, randomized placebo-controlled trial including 261 men. The Male osteoporosis study (MALEO, CL3-12911-032) assessed the efficacy and safety of strontium ranelate in men with primary osteoporosis. Primary endpoint was relative changes from baseline of lumbar bone mineral density (BMD). BMD increased significantly in the strontium ranelate group compared to placebo from baseline to Month-24 at the lumbar (L2-L4) by 9.8%±1.1 ($p<0.001$), femoral neck by 3.3%±0.9 ($p<0.001$) and total hip by 3.7%±0.8 ($p<0.001$).

The efficacy of strontium ranelate in the treatment of osteoarthritis is currently under evaluation at the CHMP.

Characterisation of Benefits

The anti-fracture efficacy previously demonstrated in postmenopausal women can be generalized to men at risk of fracture.

Discussion on benefits

During an article 20 referral in March 2012, the CHMP confirmed the favorable benefit/risk balance of strontium ranelate under normal conditions of use, subjected to changes to the product information regarding risk for VTE and serious skin reactions.

It was acknowledged that the benefits of strontium ranelate had been demonstrated in clinical trials, which sufficiently demonstrated efficacy on the primary endpoints of clinically significance for vertebral and hip fractures in post-menopausal women.

During the reporting period, strontium ranelate has been granted with an extension of indication in osteoporotic men at high risk of fractures. The benefit/risk ratio has been considered as favourable and comparable to that observed in post-menopausal women. An observational 3-year cohort survey will be carried-out in osteoporotic men treated with strontium ranelate to evaluate the incidence of fractures and the adherence and tolerability.

Strontium ranelate has been shown to significantly reduce fracture risks at vertebral, non-vertebral and hip sites in post-menopausal women with osteoporosis, over 3 years with confirmation over 5 years and maintenance of effect over 10 years. Its mechanism of action is different from bisphosphonates, maintaining bone turnover, which for long term use, could be a beneficial effect.

6. Benefit-risk balance

The following tables summarize the main efficacy and safety outcomes.

Table 13 - Synthesized efficacy data from PMO women Phase II-III studies:

	S12911 2g	**Placebo**
New radiological vertebral fracture	N=2924, 9782.2 PY*	N=2945, 9852.6 PY*
n (%)	508 (17.4)	663 (22.5)
Per 1000 PY	51.9	67.3
OR [95% CI]	0.72 [0.64 ; 0.82]	

Clinical fractures:	N=3748, 12621.6 PY*	N=3711, 12642.7 PY*
Non vertebral fractures		
n (%)	426 (11.4)	492 (13.3)
Per 1000 PY	33.8	38.9
OR [95% CI]	0.84 [0.73 ; 0.96]	

Hip fracture		
n (%)	109 (2.9)	114 (3.1)
Per 1000 PY	8.6	9.0
OR [95% CI]	0.95 [0.72 ; 1.23]	

Table 18 - Pooled safety data from PMO women Phase II-III studies:

	S12911 2g N=3803, 11269.6 PY*	**Placebo** N=3769, 11250.1 PY*
Serious cardiac disorders		
n (%)	262 (6.9)	215 (5.7)
Per 1000 PY	23.3	19.1
OR [95% CI]	1.22 [1.02 ; 1.48]	

Myocardial Infarction		
n (%)	64 (1.7)	40 (1.1)
Per 1000 PY	5.7	3.6
OR [95% CI]	1.6 [1.07; 2.38]	

Embolic & thrombotic events		
n (%)	306 (8.0)	261 (6.9)
Per 1000 PY	27.2	23.2
OR [95% CI]	1.18 [0.99; 1.40]	

Venous embolic & thrombotic events		
n (%)	71 (1.9)	47 (1.2)
Per 1000 PY	6.3	4.2
OR [95% CI]	1.51 [1.04; 2.19]	

** The differences in patient years in the table depend on the following: Follow-up time for vertebral fractures is to last X-ray performed. For clinical fractures, the efficacy data was collected 6 months after last study drug intake which was not the case for safety data. See further comments under Q 1.*

Benefits

Beneficial effects

Postmenopausal women

In the largest placebo-controlled study of post-menopausal osteoporotic patients, TROPOS (N=5091), the absolute non-vertebral fracture risk reduction over 3 years in strontium ranelate treated patients was 1.7% compared to placebo (p=0.04). There was a significant absolute reduction in hip fractures in a subgroup of women >74 years at a high risk for fracture of 1.9% (p=0.046). The absolute reduction

in vertebral fracture incidence was 7.5%. The beneficial effects on vertebral fractures were confirmed in SOTI study (N=1649) with a 12% absolute incidence risk reduction from 33% to 21% over 3 years.

When fracture data from all PMO women studies is synthesized, the reduction of non-vertebral fractures in strontium ranelate treated patients compared to placebo was 5.1 events per 1000 PY and new vertebral fracture 15.4 events per 1000 PY. The reduction in non-vertebral fractures consisted mainly of fractures in ribs-sternum 2.3 events, pelvic-sacrum 1.6 events and humerus 1.2 events per 1000 PY. There was no obvious difference in hip fractures.

Men with osteoporosis

The approval of male indication was based on bone mineral density data that corresponded to BMD changes in PMO women. Only 22 fractures occurred in the MALEO study (N=173) with no obvious differences between treatment groups.

Uncertainty in the knowledge about the beneficial effects

Osteoporosis treatment involves -beyond medication- lifestyle changes including diet, physical activity and smoking cessation. In addition, different fall prevention measures can considerably reduce the fracture risk but comparisons of efficacy between these non-pharmaceutical interventions with specific anti-osteoporotic treatments are difficult.

The reported fracture risk reductions are greatly influenced by the baseline risks in the studied populations and other confounders, for example calcium and vitamin D supplementation.

Risks

Unfavourable effects

When safety data from pooled placebo-controlled studies of post-menopausal osteoporotic patients (OSA 2011) is synthesized, there was no obvious difference in overall SOC cardiac disorders or cardiovascular death or overall mortality. However, an increase in serious cardiac disorders of 4.1 events per 1000 PY was observed between the strontium ranelate treated group and placebo. Review of the requested SMQ data show a significant increase in SMQ myocardial infarction of 2.1 events per 1000 PY, OR 1.6 (1.07- 2.38) and a tendency to increase in the SMQ Ischaemic Heart disease 3.4 events per 1000 PY, OR 1.13 (0.96-1.33).

Venous thromboembolism (VTE) has been an identified risk of strontium ranelate since its approval. In OSA 2011, the borderline significant increase in strontium ranelate in SMQ Embolic & thrombotic events was 4.0 events per 1000 PY. For venous embolic and thromboembolic events the OR was significantly higher in the strontium ranelate treated patients OR 1.51 (1.04-2.19). The risk of thromboembolic events was especially high in patients >80 years.

Findings from other study populations, male osteoporotic patients and osteoarthritis patients give some support for an increased cardiac risk of strontium ranelate. For instance, a numerical tendency of increase of serious cardiac disorders compared to placebo of 12.7 events per 1000 PY in osteoporotic men and 8.2 events per 1000 PY in osteoarthritis patients was observed in strontium ranelate treated patients. The smaller numbers of patients make these observations uncertain compared to the data in PMO women.

Among an estimated post-marketing exposure of approximately 3.4 million patient years, 2074 reports have been received on hypersensitivity reactions associated with strontium ranelate. A total of 71 cases were confirmed as DRESS possibly related to Strontium ranelate and 21 cases were confirmed as TEN or SJS. Serious skin disorders are labeled as very rare and as rare in Asian populations.

Other labeled unfavorable effects of strontium ranelate include disturbances in consciousness (common), musculoskeletal pain and creatine kinase increase (common), nausea (common), seizures (uncommon), hepatitis (frequency unknown) and bone marrow failure (frequency unknown).

Uncertainty in the knowledge about the unfavourable effects

Mechanistic considerations:

Given the thrombotic potential of strontium ranelate illustrated by the identified risk for venous thromboembolism, there is a possible mechanistic rationale for a wider cardiovascular risk.

Strontium ranelate treatment was associated with moderate increased levels of factor VIII in healthy postmenopausal females and with clinically significant elevations (>200%) in osteoarthritis patients (8.5% in SrRan 2g vs. 3.0% in placebo). No differences were observed in the male osteoporosis study but the number of patients was small. Epidemiological studies have suggested that increased Factor VIII levels could be associated with athero-thrombotic events.

There are conflicting published results on the relationship between calcium and ischemic cardiac events. A recent meta-analysis of 11 trials (11921 subjects) found an increase in myocardial infarction in patients receiving daily calcium. Strontium could theoretically have a similar calcium-like effect on cardiac events.

Myocardial infarction (MI) in PMO studies- only an isolated signal?

In randomised placebo-controlled studies (PMO women, male osteoporosis and osteoarthritis), a consistent numerical increases in serious cardiac disorders, myocardial infarction, ischaemic heart disease and DVT were observed in all treatment indications.

The AE data for overall SOC cardiac disorders and cardiovascular death including sudden death did not show similar consistency in randomized placebo controlled studies. The reason for this can only be hypothesized upon. These studies were not designed to assess cardiovascular safety and the cardiac events were non-adjudicated. However, myocardial infarction has well established criteria in clinical practice, in contrast to overall cardiac disorders which are clinically not as well-defined. Also symptoms of non-MI ischaemic heart disease may be diffuse in women and clinically challenging to diagnose. Among the serious cardiac events or MI, 17.5 % of patients stopped the study treatment because of the event. No specific follow up was set up for these patients, which means that no mortality data after study discontinuation was collected or included in the outcome cardiovascular death. Consequently, the SMQ MI narrow data could be considered as the most reliable of the cardiac data outcomes.

Cerebrovascular disease was not overrepresented in strontium ranelate treated patients talking against universal thrombotic potential of strontium ranelate. This finding is in line with the potential mechanistic considerations on calcium-like effects: calcium supplementation has been associated with none or non-significant increases in stroke in studies that found an association with myocardial infarctions and ischemic cardiac disease. Irrespective, it is difficult to disregard the MI data based on a lack of signal for cerebrovascular disease.

There were no major discrepancies in the cardiovascular risk factors at baseline in main PMO studies in the strontium ranelate group as compared to the placebo group which is reasonable for these large studies.

MI is not a labeled adverse event for strontium ranelate and occurs commonly in the elderly population. Moreover, the increased risk for MI risk is not closely time-related to the treatment start with strontium ranelate but constant over time. Therefore, it is unlikely that a MI occurring several

months or years after treatment start with strontium ranelate in these elderly patients with multiple concomitant diseases is reported as an adverse event in signal detection databases. This might explain why no signal was observed for MI in post marketing surveillance in contrast to clinical studies.

An observational 3 –year cohort of 12702 PMO women treated with strontium ranelate with focus on all safety concerns had a low incidence of reported MI events (1.3 per 1000 PY). The cohort did not show an increased incidence of MI in comparison to historical Framingham cohort incidence and prevalence chart book on cardiovascular and lung disease, 2006 (incidence between 3.2 and 11 per 1000 PY) However, the evidence quality from this type of study and comparisons is considered weak compared to large randomized placebo controlled trials and not enough to reject the hypothesis of an increased risk of MI.

In a nested case-control study using CPRD database, the risk of myocardial infarction, MI with hospitalization and cardiovascular death was studied in PMO women. The complete final study report will be submitted in May and consequently a full study assessment is not possible at this time. The main results indicate that compared to osteoporosis patients without a specific anti-osteoporotic treatment, there was no increased cardiac risk associated with strontium ranelate treatment. Compared to current alendronate users, however, the strontium ranelate users had a numerically higher odds ratio for MI, MI with hospitalization and borderline significant higher risk for cardiovascular death OR 1.27 (1.00-1.61).

Strontium ranelate has been shown to decrease the risk of hip fracture in a subgroup of women >74 years at high risk for fracture. The risk of unfavorable effects in this subgroup is unclear. However, after the art. 20 referral finalized in March 2012, new warnings for patients aged more than 80 years and at risk for VTE were introduced.

Regarding VTE, new contraindications for current or previous VTE, including deep vein thrombosis and pulmonary embolism as well as temporary or permanent immobilisation due to e.g. post-surgical recovery or prolonged bed rest were introduced following the art. 20 referral finalised in March 2012. Those are intended to reduce the risk for VTE in the target population. The impact of these measures on reduction of risk is unclear. However, data recently evaluated within the type II variation for a new indication in osteoarthritis raise some concern. Despite that Medical history of VTE (including pulmonary embolism) or high risk of venous thromboembolism were exclusion criteria in the present study, there was a numerical increase in VTE: 5 events /548 for the 1 g SrRan group, 3 events /564 events for the 2 g SrRan group, compared with one event /556 in the placebo group.

Balance

Importance of favourable and unfavourable effects

Radiological vertebral fractures are a common finding in postmenopausal women and usually asymptomatic. A typical symptomatic vertebral fracture causes acute pain and decreased mobility that lasts about one month. Radiological vertebral fractures can be considered as important markers of osteoporosis severity that is shown to be associated with increased risk of future clinical fractures, reduced quality of life, morbidity and mortality.

Fractures that require surgery are the most dangerous aspect of osteoporosis. Hip fracture and the following surgery, in particular, is associated with serious risks, permanent disability and increased mortality.

Myocardial infarction is a potentially life threatening condition that often requires invasive treatments, several days of hospitalization and life-long medication. Deep vein thrombosis and pulmonary

embolism are also potentially life threatening conditions requiring acute treatments and close long-term follow up and a risk of hemorrhagic adverse events. Serious skin adverse reactions are rare but unpredictable adverse events with a high mortality.

The benefit-risk balance of strontium ranelate was discussed during an article 20 referral in March 2012 with focus on VTE and serious skin reactions. This procedure resulted in additions of new warnings and contraindications for strontium ranelate. The cardiac safety of strontium ranelate in PMO women has been assessed previously based on the pivotal TROPOS and SOTI studies but this was not the primary concern in the 2012 referral. However, after the 2012 referral, new safety data from clinical studies of osteoporotic men and osteoarthritis patients has become available. These data raised additional concern on cardiac safety and motivated the current thorough overall benefit-risk evaluation of all available data.

Benefit-risk balance

Discussion on the benefit-risk assessment

Comparisons of number of events per 1000 PY indicate that preventing one non-vertebral fracture (including fractures not requiring surgery) with strontium ranelate treatment in post-menopausal women roughly corresponds to the risk of causing one serious cardiac disorder or a thromboembolic event (before introducing contraindications for patients with current or previous VTE or with temporary or permanent immobilisation). In addition, the strontium ranelate treatment is associated with rare but serious adverse events such as serious skin reactions. The prevention of usually asymptomatic radiological vertebral fractures is considered to have a lower immediate clinical importance compared to the conditions above.

The studies on male osteoporosis and osteoarthritis give some support to increased risk of ischaemic heart disease and myocardial infarction associated with strontium ranelate treatment.

Regarding risk minimization, it is reasonable to try to reduce the target population by excluding patients with high risk for ischemic cardiac disorders. This could also be supported by an argument put forward by the MAH that the increased MI risk was mainly due to results from the TROPOS study, which included patients at higher age and higher rate of cardiac co-morbidities.

In light of the identified serious risks, it is also reasonable to restrict the indication to the patients who are most likely to benefit from the treatment i.e. those with severe osteoporosis and at highest risk of fracture. However, it should be remembered that the risk profile is partly overlapping for ischemic cardiac disorders and for osteoporosis.

The MAH proposed at the PRAC April 2013 oral explanation following addition in section 4.4 of the SPC: "Protelos is thus not recommended for female and male patients with history of ischemic disease including myocardial infarction. Protelos should not be initiated in patients with uncontrolled blood pressure." This was not considered sufficient.

The PRAC recommends a restriction of the approved indications to treatment of severe osteoporosis in postmenopausal women at high risk for fracture, and treatment of severe osteoporosis in men at increased risk of fracture. The decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks in light of the therapeutic benefit. In addition, the PRAC recommends that the product should not be used in patients with established, current or history, of ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and/or uncontrolled hypertension. Moreover, patients with significant risk factors for cardiovascular events (e.g.

hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration.

Furthermore, the PRAC recommends that the product should only be prescribed by physicians with experience in the treatment of osteoporosis and that before starting treatment and thereafter at regular intervals, patients should be evaluated with respect to risk of developing cardiovascular disease. In addition, the PRAC recommends that the prescribers are informed of these changes to the product information via a Direct Healthcare Professional Communication (DHPC). The MAH should also perform a study to evaluate the compliance with the new prescribing recommendations.

Providing these restrictions recommended by the PRAC, the benefit/risk balance of strontium ranelate remains favorable.

Conclusions

In addition to previously identified serious risks, an increased risk for myocardial infarction in osteoporosis patients has now been identified. The PRAC recommends restricting the use of strontium ranelate to patients with higher estimates of fracture prevention in comparison to the identified cardiac and vascular safety risks. On the basis of the current assessment, the benefit/risk balance of strontium ranelate remains favorable in the identified restricted population.

7. Final assessment conclusions and actions

Data submitted in the present PSUR raise concern regarding cardiovascular safety beyond the already recognized risk for venous thromboembolism. An increased risk for serious cardiac disorders, including myocardial infarction has now been identified. This conclusion is predominantly based on data from pooled placebo-controlled studies in post-menopausal osteoporotic patients (3,803 patients treated with strontium ranelate, corresponding to 11,270 patient years of treatment, and 3,769 patients treated with placebo, corresponding to 11,250 patient years of treatment). In this data set, a significant increase of serious cardiac disorders (6.9% versus 5.7% OR 1.22 [1.02 ; 1.48]) and of myocardial infarction (1.7% versus 1.1 %), with a relative risk of 1.6 (95% CI = [1.07 ; 2.38]), has been observed in strontium ranelate treated patients compared with placebo treated patients with no impact on mortality. Further, there was an imbalance of such events both in a study in osteoporotic men, and in a study in osteoarthritis. The smaller numbers of patients make these observations uncertain compared to the data in PMO women. In addition, there is a possible mechanistic rationale for an increased risk for serious cardiac disorder including myocardial infarction.

Taking all currently available efficacy and safety data, including the newly identified risk for serious cardiac disorders presented within this PSUR procedure into account, the PRAC recommends to introduce risk minimization measures to reduce the target population by excluding patients with high risk for ischemic cardiac disorders, and to restrict the indication to the patients who are most likely to benefit from the treatment i.e. women with severe osteoporosis and at high risk of fracture and men with severe osteoporosis at increased risk of fracture. The PRAC considers that the introduction of these measures taken together with further steps as outlined below allows the identification of a patient population for which the benefit/risk remains favorable.

These additional measures include the following:

The decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks. In addition, the PRAC recommends that the product should not be used in patients with established, current or history, of ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and/or uncontrolled hypertension. Moreover, patients with significant risk

factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration.

Furthermore, the PRAC recommends that the product should only be prescribed by physicians with experience in the treatment of osteoporosis and that before starting treatment and thereafter at regular intervals, patients should be evaluated with respect to risk of developing cardiovascular disease.

In addition, the PRAC recommends that the prescribers are informed of these changes to the product information via a Direct Healthcare Professional Communication (DHPC).

The MAH should also perform a study to evaluate the compliance with the new prescribing recommendations.

Given the overall safety profile, characterized by various serious risks including venous thromboembolism, cardiac disorders and skin reactions; and particularly given the need for a study that will evaluate the compliance with the new prescribing information, the product should be subject to additional monitoring.

The next PSUR should cover the period from 22 September 2012 to 21 September 2013 and be submitted within 70 days of the data lock point.

The risk management plan (RMP) should be revised to include serious cardiac disorders including myocardial infarction as an important identified risk. The non-interventional safety study should be added to the Pharmacovigilance Plan, including time lines for submission of a protocol and a final study report. The DHPC should be added among risk minimization measures. Furthermore, all relevant sections of the RMP should be revised to reflect this new important identified risk.

The PRAC concluded that, on the basis of the current assessment, the benefit/risk balance of strontium ranelate remains favourable in the identified restricted population. However, the PRAC considers that, in view of the newly identified risk of serious cardiac disorders including myocardial infarction, and in order to allow all available data on efficacy and safety to be taken into account, the benefit/risk balance of medicinal products containing strontium ranelate should be further evaluated in an expedited timeframe.

8. Recommendations

Based on the PRAC review of data on safety and efficacy submitted during this PSUR procedure, the PRAC considers by majority decision that the risk-benefit balance of medicinal products containing the active substance strontium ranelate remains favourable but recommends that the terms of the marketing authorisations should be varied as follows:

Update of section 4.1 of the SmPC to restrict the indication to patients with severe osteoporosis, and in postmenopausal women, at high risk of fractures. In section 4.1, it is also reminded that the decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks. Update of section 4.3 of the SmPC to contraindicate the use of strontium ranelate in patients with established, current of history of, ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and / or uncontrolled hypertension. In addition, update of sections 4.2, 4.4 and 4.8 of the SmPC to establish that the treatment should only be initiated by a physician with experience in the treatment of osteoporosis, to add a warning on cardiac ischaemic events and to add myocardial infarction as a common adverse reaction.

The Package leaflet is updated accordingly.

In addition, the PRAC recommends the following changes to the conditions of the MA:

- Conditions regarding the supply and use: restricted medical prescription.

- Obligation to conduct post-authorisation measures: study to assess the effectiveness of the agreed risk minimisation measures.

The amendments recommended to be introduced to the product information and conditions to the marketing authorisation are detailed in Annex 1 and Annex 2.

In addition the PRAC recommends that the prescribers are informed of these changes to the product information via a Dear Healthcare Provider Communication (DHPC).

Further the PRAC recommends that the product should be subject to additional monitoring.

The PRAC also recommends that in view of the newly identified risk of serious cardiac disorders including myocardial infarction, and in order to allow all available data on efficacy and safety to be taken into account, the benefit/risk balance of medicinal products containing strontium ranelate should be further evaluated in an expedited timeframe.

In addition, the MAH should also address the following issues in the next PSUR:

- An increase in serious unlisted events in PSUR 12 should be followed up and the MAH is requested to present a summary table, including the findings in the PSUR 13 period.

In addition, the MAH should submit an updated RMP within the next relevant procedure in order to address the following issues:

- The RMP should be updated to reflect the conclusions of the PRAC after the evaluation of the PSUR.
- Six signals previously categorized as potential risk were considered as false signals and closed. However, the PRAC considers that "interstitial nephritis, "depression", "bone sarcoma" and "pancreatitis" should remain in the potential risk list.

9. List of annexes

1. Recommended changes to the product information
2. Recommended changes to the conditions of the marketing authorisation

ANNEX 1

RECOMMENDED CHANGES TO THE PRODUCT INFORMATION

The following changes to the product information of medicinal products containing the active substance strontium ranelate are recommended:

Summary of product characteristics

- Section 4.1

"Treatment of severe osteoporosis in postmenopausal women at high risk for fracture to reduce the risk of vertebral and hip fractures (see section 5.1).

Treatment of severe osteoporosis in adult men at increased risk of fracture (see section 5.1).

The decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks (see sections 4.3 and 4.4)."

- Section 4.2

The following statement should be added:

"Treatment should only be initiated by a physician with experience in the treatment of osteoporosis."

- Section 4.3

The following contra-indications should be added:

"Established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

Uncontrolled hypertension."

- Section 4.4

The following warning should be added:

"Cardiac ischaemic events
In pooled randomised placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase in myocardial infarction has been observed in PROTELOS treated patients compared to placebo (see section 4.8).
Before starting treatment and at regular intervals, patients should be evaluated with respect to cardiovascular risk.
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration (see sections 4.3 and 4.8).
Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or if hypertension is uncontrolled (see section 4.3)."

- Section 4.8

The following statement should be added:

"In pooled randomised placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase of myocardial infarction has been observed in PROTELOS treated patients as compared to placebo (1.7% versus 1.1 %), with a relative risk of 1.6 (95% CI = [1.07 ; 2.38])."

In addition, "myocardial infarction" at a frequency of common should be added to the table of adverse reactions, stating that the percentage of patients experiencing the adverse reaction in the strontium ranelate group were 1.7% compare to 1.1% in the placebo group.

The following foot note should be added:

[d] In pooled placebo-controlled studies of post-menopausal osteoporotic patients, strontium ranelate treated patients (N=3803, 11270 patient years of treatment) compared to placebo (N=3769, 11250 patient years of treatment)

The following text should be added in accordance to the QRD template:

"Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V"

Package leaflet

The PRAC agreed wordings for the package leaflet in line with the changes agreed for the SmPC

ANNEX 2

RECOMMENDED CHANGES TO THE CONDITIONS OF THE MARKETING AUHTORISATION

The following changes to the conditions of the marketing authorisations of medicinal products containing the active substance strontium ranelate are recommended:

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Periodic Safety Update Reports

  The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

OBLIGATION TO CONDUCT POST-AUTHORISATION MEASURES

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Non-interventional safety study to evaluate the effectiveness of the applied risk minimisation measures, including a description of the treated patient population in everyday clinical practice	*Q2 2014*

Attachments

PRAC Divergent Position

The undersigned members of PRAC did not agree with the PRAC's opinion recommending that the Marketing Authorisation should remain for Protelos/Osseor.

The reasons for divergent opinion were as follows:

- With respect to benefit, when fracture data from randomized, placebo-controlled studies in postmenopausal women were synthesized, the reduction of non-vertebral fractures in strontium ranelate treated patients compared to placebo was 5.1 events per 1000 patient years (pty) and new vertebral fracture 15.4 events per 1000 pty. The reduction in non-vertebral fractures consisted mainly of fractures in ribs-sternum, pelvic-sacrum and humerus. There was no obvious difference for hip fractures. Thus, efficacy is considered of modest magnitude, particularly regarding the most serious types of fractures.
- In the current PSUR assessment procedure, it has been concluded that the available evidence indicates that serious cardiac disorders including myocardial infarction represent a newly identified risk. This conclusion is predominantly based on the same data set as described in the previous paragraph on benefit. In this data set, a significant increase of serious cardiac disorders of 4.1 events per 1000 pty was observed for the strontium ranelate treated group compared with placebo. Also for myocardial infarction, a significant increase was observed, corresponding to 2.1 additional events per 1000 pty (relative risk of 1.6 [95% CI (1.07-2.38)]. Furthermore, there was an imbalance of such events both in a study in osteoporotic men, and in a study in osteoarthritis. In addition, there is a plausible mechanistic rationale for an increased risk for serious cardiac disorder including myocardial infarction. It was therefore concluded that the consistent numerical increases in serious cardiac disorders, myocardial infarction, ischaemic heart disease and deep vein thrombosis observed in randomised placebo-controlled studies in all treatment indications (osteoporosis in post-menopausal women, male osteoporosis and osteoarthritis), considered in the context of a possible mechanism, provide consistent evidence of concern regarding cardiovascular safety. On this basis, the Committee agreed that the available data from clinical studies support the inclusion of 'myocardial infarction' as an adverse reaction in the SmPC with a frequency of 'common'.
- Strontium ranelate is also associated with other, already identified and labeled, undesirable effects, including venous thromboembolic events (VTE), serious skin reactions (including DRESS, SJS, and TEN), disturbances in consciousness, seizures, hepatitis and blood cytopenic disorders.
- As regards the benefit-risk balance, comparisons of number of events per 1000 patient years indicate that preventing one non-vertebral fracture (including fractures not requiring surgery) with strontium ranelate treatment in post-menopausal women roughly corresponds to the risk of causing one serious cardiac disorder or a thromboembolic event. In addition, strontium ranelate treatment is associated with rare but serious adverse events such as serious skin reactions. The prevention of usually asymptomatic radiological vertebral fractures is considered to have a lower immediate clinical importance compared to these serious adverse events.
- There is considerable uncertainty regarding the evidence on benefit in support of the newly proposed indication in severe osteoporosis, as well as in relation to the validity and practicability of the proposed risk minimization measures with respect to the restricted indications, contraindications and warnings, to minimize the risk of myocardial infarction, VTE,

and serious cardiac disorders in particular due to the fact that certain risk factors for these undesirable effects are overlapping with risk factors for osteoporosis and the treatment will be used chronically.

Taking all these aspects into account, the benefit / risk balance of Protelos/Osseor is negative. A suspension of the MA is recommended, while further support for a positive benefit/risk balance in a restricted population is gathered.

London, 11 April 2013

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Almath Spooner (Ireland)	Jean-Michel Dogné (Belgium)
……	……
Isabelle Robine (France)	Julia Pallos (Hungary)
……	……
Carmela Macchiarulo (Italy)	Jolanta Gulbinovic (Lithuania)
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Miguel-Angel MACIA (Spain)	Qun Ying Yue (Sweden)
……	……
Herve Le Louet (French Expert)	Jane Ahlqvist Rastad (Swedish Expert)