1. ABSTRACT

Title	**European Program of Post-Authorization Safety Studies for Protelos®/Osseor® through EU-ADR Alliance: RMM Analyses (part of Final Report)** Study number: CLE-12911-046 Final report version 1 Author: Dr. Daniel Prieto-Alhambra Date: 23 November 2017
Keywords	1.Strontium Ranelate; 2.Drug Utilization; 3.Pharmacoepidemiology; 4.Risk minimization measures.
Rationale and background	In the frame of 13th PSUR assessment of Strontium ranelate (Protelos®/Osseor®), data submitted raised concern regarding cardiovascular safety beyond the already recognized risk for venous thromboembolism. As a result, risk minimization measures (RMM) were recommended by CHMP including new contraindications (current or past history of 1.ischaemic heart disease, 2.peripheral arterial disease, 3.cerebrovascular disease; and/or 4.uncontrolled hypertension), and restricted indications (1.severe osteoporosis at high risk for fracture; 2. Initiation by a physician with experience in the treatment of osteoporosis). These were disseminated in a DHPC in May 2013. Additionally, an overall benefit/risk review under Article 20 of regulation (EC) No 726/2004 started in May 2013 and finalized on 20 February 2014 led to a restriction of the indication to postmenopausal women and men with severe osteoporosis at high risk of fracture for whom alternative anti-osteoporosis treatment is not possible, disseminated (DHPC) in March 2014.
Research question and objectives	<u>RMM Effectiveness Study</u> **1. To characterize utilization patterns of strontium ranelate (SR) in: up to May 2013 (first DHPC), between June 2013 and March/2014 (second DHPC), and from April 2014 onwards.** **2. To estimate the prevalence of contraindications in SR users during the same three periods.** **3. To calculate the prevalence of SR users who fulfil the new indications (after imposition of new restrictions of use) for SR therapy in the same three periods.** <u>Safety Study</u> 1. To estimate the incidence rates of AMI, cardiovascular death, and VTE in SR users with and without contra-indications prior and after June 2013. 2. To compare the risk of AMI, cardiovascular death, and VTE between incident users of SR and incident users of oral bisphosphonates without contra-indications, both before and after June 2013. ***The current final report provides results for the three objectives (in***

	bold) within the 'RMM Effectiveness' study. The Safety study findings are detailed in a separate report.
Study design	Multi-national multi-database population-based cohort. The study period for these analyses is split in three periods for the analysis of RMM Effectiveness: 1. Up to May 2013 (first DHPC and SmPC revision): **Reference** 2. From June 2013 to March 2014 (second DHPC and SmPC revision): **Transition** 3. and from April 2014 onwards (until December /2016 for all databases, except August/2016 for THIN-UK): **Assessment period**
Setting	Routinely collected health data from databases in the EU-ADR Alliance. The EU-ADR Alliance is a network of research institutes that conduct pharmaco-epidemiological research. For this study data from 5 EU countries are used: Denmark (DK), Italy (IT), Netherlands (NL), Spain (ES), and United Kingdom (UK) (see below).
Subjects and study size, including dropouts	The study population for this final report comprises the entire source population for population-level analyses, as well as all identified users of SR for the same analyses at the patient level.
Variables and data sources	**STUDY OUTCOMES** Contra-indications*:* 1. Venous thromboembolism (VTE) 2. Ischaemic heart disease (IHD) 3. Peripheral arterial disease (PAD) 4. Cerebrovascular disease (CVD) 5. Uncontrolled hypertension (UH) New indications/restrictions for use: 1. Experienced prescriber 2. Treatment not in first line 3. Severe osteoporosis 4. All new indications fulfilled 5. Any of the new indications fulfilled **DATA SOURCES** Data from 5 electronic healthcare databases (all listed in ENCePP registry of data sources) have been obtained, namely: 1. The Integrated Primary Care Information Project (IPCI) from the Netherlands 2. The Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) from Catalonia, Spain 3. The Health Improvement Network (THIN) from the UK

	4. Aarhus Database (AUH) from Denmark 5. And The HSD-Thales database from Italy
Results	**<u>Population-level SR utilization patterns</u>** Almost 143.5 million person-years (py) of observation, and a total of 77,284 SR users (89.6% women) were included. Overall population-based incidence rates (IR) of SR use have decreased from 7.35/10,000 py [95%CI 7.35-7.35] in the Reference to 0.22/10,000 py [0.22-0.22] in the Assessment period. Similarly, prevalence of SR use has dropped from 62.63/10,000 py [95%CI 62.37-62.89] in the Reference to 8.54/10,000 py [8.45-8.62] in the Assessment period. **<u>Patient-level SR utilization</u>** One-year SR therapy stopping has increased from 82.7% [82.4-83.0%] in Reference to 86.3% [83.5-88.7%] in the Assessment period. **<u>Prevalence of contraindications amongst SR users</u>** The prevalence of any contraindication has decreased both amongst incident and prevalent users of SR: from 2.16% [2.06 to 2.27%] in the Reference to 1.75% [1.03 to 2.97%] in the Assessment period (incident users); and from 2.28% [2.24 to 2.31%] in the Reference to 1.61% [1.48 to 1.76%] in the Assessment period (for prevalent users) respectively. **<u>Prevalence of new indications amongst SR users</u>** The proportion of incident users of SR fulfilling all or any (at least one) of the new restrictions of use has increased from 13.71% [13.47 to 13.96%] to 26.78% [23.72 to 30.08%] and from 92.83% [92.64 to 93.01%] to 97.04% [95.56 to 98.04%] respectively in the Assessment period. Similar figures are seen for prevalent users of SR fulfilling all or at least one of these restrictions, with proportions increasing from 17.44% [17.35 to 17.53%] to 28.70% [28.20 to 29.20%] and from 96.89% [96.84 to 96.93%] to 97.11% [96.92 to 97.29%] respectively. *Note on interrupted time series* Low incidence and prevalence in the assessment period and high auto correlation prevented the completion of this analysis.
Discussion	The RMM disseminated in May 2013 and March 2014 have had a clear impact in terms of both population and patient-level SR drug use: 1.both the incidence and prevalence of use have decreased in the contributing data sources from Denmark, Italy, Netherlands, Spain, and the United Kingdom. Data from 2016 confirm the decline in use observed in the two submitted interim reports. 2.at the patient-level, persistence with SR has decreased in the Assessment compared to the Reference period. AND 3.finally, the prevalence of contraindications has dropped substantially whilst the proportion of SR users fulfilling the new indications/restrictions of use increased after the proposed RMMs. In conclusion, there is a reduced use of SR at the population (incidence

	and prevalence of use) and patient-based (persistence) levels after the RMMs. In addition, we observe an increase in 'appropriateness' of use of the drug as per newly imposed conditions (indication and contraindications) of use following the dissemination of RMMs. The parallel Safety report cohort analyses suggest that these changes (increase in proportion of patients with no contra-indications after the RMM) result in an overall population reduction in potential risk: rates of AMI, VTE and cardio-vascular death were 4-5-fold lower in those without contra-indications.
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2. ABSTRACT

Title	**European Program of Post-Authorization Safety Studies for Protelos®/Osseor® through EU-ADR Alliance: Safety Analyses (part of Final Report)** Study number: CLE-12911-046 Final Report V1 Authors: M Sanni Ali, Daniel Prieto-Alhambra Date: 23 November 2017
Keywords	1.Strontium Ranelate; 2.Drug Safety; 3.Pharmacoepidemiology.
Rationale and background	Strontium ranelate (Protelos®/Osseor®) was authorized in the European Union in 2004 and 2012 for the treatment of osteoporosis in postmenopausal women and adult men at increased risk of fracture respectively. In the frame of 13th PSUR assessment, cardiovascular safety concerns were raised beyond the previously recognized risk for venous thromboembolism. As a result, an increased risk for serious cardiac disorders, including myocardial infarction was identified and risk minimization measures (RMM) targeting this issue were recommended by the CHMP and disseminated (DHPC) in May 2013. In addition, an overall benefit/risk review under Article 20 of regulation (EC) No 726/2004 started in May 2013 and was finalized on 20 February 2014, leading to a restriction of the indication. A new DHPC was hence disseminated in March 2014 to include this information, and the current PASS was set up. The overarching aims of the study were: **1.** To study the effect of the RMMs for Strontium Ranelate **2. To estimate and compare the risk of cardiac and thromboembolic events in incident users of SR compared to incident users of bisphosphonates**. ***This report provides results for the second of these objectives. The RMM Effectiveness findings are detailed in a separate document.***
Research question and objectives	1. To estimate the incidence rates of cardiac and thromboembolic events in SR users with and without contra-indications prior and after June 2013 (Objective 1).

	2. To compare the risk of cardiac and thromboembolic events between incident users of SR and incident users of oral bisphosphonates (BP) without contra-indications, both before and after June 2013 (Objective 2).
Study design	Multi-national multi-database approach with: **1. Population-based cohort study** (Objective 1) including incident users of SR or BP in the study period. **2. Nested matched case-control analyses** (Objective 2) of cardiac and thrombo-embolic risks nested in the cohort above. **3. Meta-analysis** (of database-specific case-control findings) and **mega-analysis** (of all case-control sets combined).
Setting	The study was conducted using routinely collected health care data from 5 databases that participate in the EU-ADR Alliance: Denmark (DK), Italy (IT), the Netherlands (NL), Spain (ES), and the United Kingdom (UK). The EU-ADR Alliance is a network of research institutes that conduct pharmaco-epidemiological research.
Subjects and study size, including dropouts	**Objective 1 (Cohort)** included all subjects aged 50+ years with at least one year of valid data and defined as incident (1-year wash-out) users of SR or BP during the study period. SR users were analysed – as planned per protocol- for this first Objective. **Objective 2 (Case-control)** included cases (acute myocardial infarction, venous thrombo-embolism, or cardio-vascular death) and up to 10:1 matched controls (by age, cohort entry, index date, gender, and data source) pooled from the above cohort without any of the newly defined contra-indications (ischaemic heart disease, peripheral artery disease, cerebro-vascular disease, uncontrolled hypertension) or Paget's disease of bones; those with a previous history of venous thrombo-embolism were in addition excluded for the analysis of this specific outcome. **Study period**: The study period started on the year of licensing (January 1st, 2004 for all databases except 2006 for SIDIAP and December/2004 for AUH) and ended at latest data supply (end/2016 for all, except August/2016 for THIN). All analyses were conducted stratified according to period of therapy initiation (before vs from June/2013).
Variables and data sources	**STUDY EXPOSURE** Strontium ranelate (ATC M05BX03) use was compared to oral

	bisphosphonates (active comparator) (ATC M05BA04 – alendronate, M05BA06 - ibandronate, or M05BA07 - risedronate). Exposure to SR or BP was based on treatment status for each drug, and defined as current use (event while on treatment), recent use (1-180 days after cessation) or past use (181 days or more after stopping). **STUDY OUTCOMES** **6. Venous thromboembolism (VTE)** including deep vein thrombosis and pulmonary embolism as recorded in primary (HSD-IT, THIN-UK, IPCI-NL and SIDIAP-ES) or secondary care records (AUH-DK). The code lists were validated in 4 data sources (no need in AUH). Positive predictive value was high (>75%) in all, except IPCI-NL, where cases were individually confirmed using free text. **7. Acute Myocardial Infarction (AMI)** as recorded in primary (HSD-IT, THIN-UK, IPCI-NL and SIDIAP-ES) or secondary care records (AUH-DK). AMI code lists have been previously validated. 8. **Cardio-vascular-death** as either recorded in mortality registry (AUH-DK) or identified using an algorithm (death date combined with cardiovascular event code/s in the previous 2 months) and further free text validation of potential cases. **CO-VARIABLES (POTENTIAL CONFOUNDERS)** A large list of potential confounders was considered, including 1.general confounders (age, gender, calendar time, alcohol abuse, number of appointments in the previous year, use of medications), 2.known risk factors and treatments to prevent AMI/VTE, and 3.fracture risk factors. All conditional logistic regression models fitted were adjusted for a set of common confounders as identified based on clinical knowledge, uni- (confounder-outcome) and bi-variable (confounder, exposure, outcome) analyses. **DATA SOURCES** Data from 5 electronic healthcare databases (all listed in ENCePP registry of data sources) have been obtained, namely: 6. The Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) from Catalonia, Spain

	7. The Health Improvement Network (THIN) from the UK 8. Aarhus Database (AUH) from Denmark 9. The Integrated Primary Care Information Project (IPCI) in the Netherlands 10. And The HSD-Thales database from Italy
Results	A total of 68,944 SR and 401,180 BP users were eligible for the pre-RMM period (before June 2013). However, a low number of SR users (N=2,467) after the RMM (from June 2013) limited the power for post-RMM analyses, which are reported in the Appendix. All these analyses have been completed after validation of safety events in the contributing data sources. **Objective 1: Incidence Rates (IR) of Safety Events in SR users** *Venous Thrombo-embolism (VTE)* Crude IRs of VTE were higher in SR users with compared to those without contraindications. VTE IRs did not differ with SR use in those with no contra-indications, but increased (numerically) in those with SR contra-indications during current use (IR 6.33/1,000 py [95%CI 4.62-8.47]) compared to past use (IR 4.30 [3.51-5.22] respectively). *Acute Myocardial Infarction (AMI)* Crude IRs of AMI were higher amongst SR users with compared to those without contraindications; but similar during *current* SR use (1.90/1,000 person-years (py) [1.59-2.25] without, and 8.44 [6.44-10.87] with contra-indications) compared to *past* use of SR (1.91 [1.75-2.08] without; 7.84 [6.76-9.06] with contra-indications). *Cardio-vascular death (CVDeath)* Crude IRs of CVDeath also increased in subjects with compared to those without contra-indications for SR use. Here, risk of CVDeath was significantly higher also in those with no contra-indications during current (IR 0.93/1,000 py [0.72-1.19]) compared to past SR use (0.52 [0.44-0.62]). Rates were also (numerically) higher in those with contra-indications during current compared to past SR use: 5.63 [4.02-7.66] and 3.54 [2.83-4.39] respectively. **Objective 2: Nested case-control analyses** *NOTE: all findings in this section are based on meta-analysis of*

	database-specific estimates unless specified otherwise. *Venous Thrombo-Embolism* In total, 5,614 VTE cases and 56,036 controls were identified. No association was observed between current BP compared to past BP use (adjusted OR 0.97 [95%CI 0.81-1.16]). Conversely, risk seemed higher during current compared to past SR use: adjusted OR 1.30 [1.04-1.62]. Additionally, an increase in risk was seen related to current SR compared to current BP use: adjusted OR 1.24 [0.96-1.61]). These results were homogeneous (I2 0.0%; Q p-val 0.41), and similar to those obtained from a pooled mega-analysis of all available data. In sensitivity meta-analyses including cases identified in hospital data (AUH and SIDIAP linked data), no association was found between current SR compared to past SR use (adjusted OR 0.90 [0.58-1.40]) or to current BP use (adjusted OR 1.18 [0.36 – 3.92]). *Acute Myocardial Infarction* A total of 5,477 AMI cases and 54,674 matched controls were included. AMI risk was lower during current vs past BP use (adjusted OR 0.81 [0.66-0.99]), as well as during current vs past SR use (adjusted OR 0.71 [0.56-0.91]). No association was seen between current SR compared to current BP use, with adjusted OR 0.89 [0.70-1.12]. Database-specific results were homogeneous (I^2 49.0%, Q p-val = 0.10). Mega-analyses as well as sensitivity analyses based on hospital data found similar results for all three comparisons. *Cardio-vascular death* A total of 3,019 cases of CVDeath were identified, and matched to 29,871 controls. Risk seemed lower during current compared to past BP use (adjusted OR 0.60 [0.48-0.75]), as well as with current compared to past SR use (adjusted OR 0.68 [0.48-0.96]). However, this lower magnitude reduction with SR indirectly gave an increase with current SR compared to current BP use: adjusted OR 1.35 [1.02-1.80]. These results were homogeneous (I2 0.0%; Q p-val 0.89), and similar to those obtained from a pooled mega-analysis.
Discussion	No inference was possible for SR users after June/2013 given the low number of subjects starting this drug after the imposed RMMs. In a cohort analysis, crude rates of the three safety outcomes were much higher (4-5 fold) in SR users with compared to those without the imposed contra-indications. No significant differences were seen

	in the crude rates of AMI during current compared to past use of SR. Conversely, crude rates of both VTE and CVDeath appeared higher during current (compared to past) SR use in patients without contra-indications for SR. Nested case-control analyses, including only SR/BP users with no contra-indications for SR therapy, found no association between SR use and excess AMI risk, both in analyses of primary and secondary care (hospital) records. Conversely, a 30% excess risk of VTE is seen during current compared to past SR use; and a 24% excess risk is also observed with current SR compared to current BP (active comparator) use. This association was not confirmed in cases leading to hospital care, suggesting that it might concern less severe VTE events. Finally, CVDeath risk appeared reduced by 40% during current compared to past BP use, with similar findings for current vs past SR users (32%). Surprisingly (in contrast with the latter), a 35% increase was seen when current SR and current BP users were compared. These contradictory findings in the within-cohort compared to the inter-cohort analyses are intriguing: unresolved confounding by indication (ie imbalance in unobserved variables between the BP and the SR user cohorts) could potentially explain (fully or in part) the observed increase when BP and SR users are compared. In conclusion, this study shows, in patients with no contraindications for SR: 1.no excess risk of AMI; 2.a 25%-30% excess risk of VTE; and 3. inconsistent findings with CVDeath, with a reduced risk during current compared to past SR use, but an increased association when current SR and current BP users are compared. This study also demonstrates a clear reduction in rates of the proposed safety events in subjects without SR contra-indications. The accompanying RMM Effectiveness report demonstrates a substantial impact of the proposed RMMs, resulting in a reduction in the number and proportion of SR users with any of these contra-indications. Therefore, it can be concluded that the proposed RMMs have resulted in a reduction in public health risk related to SR use in the community.

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