

## PEER REVIEW HISTORY

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This paper was submitted to the JECH but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

## ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	A comparison of adverse event and fracture efficacy data for strontium ranelate in regulatory documents and the publication record
<b>AUTHORS</b>	Bolland, Mark; Grey, Andrew

## VERSION 1 - REVIEW

<b>REVIEWER</b>	Bo Abrahamsen University of Southern Denmark Institute of Clinical Research Odense, Denmark
<b>REVIEW RETURNED</b>	09-Jun-2014

<b>GENERAL COMMENTS</b>	<p>This is a clearly written and important paper with an impact on policy and decision-making. It raises issues about transparency of clinical trials and the regulatory process. I think the case is stated clearly. Among the concerns raised, the most distressing one is that of discrepant data between the regulatory reports and the scientific publications, while differences in the type of adjustment (or no adjustment) between the papers and reports could (I do not know if this is the case) be due to reporting guidelines and due to comments made by reviewers and editors in the process of journal publication.</p> <p>This aside, data should absolutely not be discrepant and I think it would be good to add a summary table to highlight the major discrepancies between studies - this can be found by the readers in table 2 but may be missed (footnotes in a busy table). Also, I don't think the abstract is clear enough in terms of mentioning discrepant data - the focus is on discrepant results, which could be statistics not raw data, so I would clarify this here too.</p> <p>I am not sure why there is an appendix of review articles that have addressed strontium. I think this can be removed without any loss of impact.</p>
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<b>REVIEWER</b>	Karl Michaëlsson Department of Surgical Sciences Uppsala University Uppsala Sweden
<b>REVIEW RETURNED</b>	09-Jun-2014

<b>GENERAL COMMENTS</b>	<p>This overview about strontium ranelate is well written and an interesting reading. Documentation of the discrepancy between officially published and unpublished serious adverse events in clinical trials is of substantial importance for both patients and health professionals.</p> <p>Some minor issues:</p> <ol style="list-style-type: none"> <li>1. P 9, line 7. Can the authors provide reference numbers to the statements (sentence beginning with “Of the 6 economic analyses, .....</li> <li>2. Is it possible to provide information on how the adverse events were defined and identified? Was a clinical events committee used in the trials? Can a change in definition of the adverse events by time in part explain the higher number of adverse events in later documentations?</li> <li>3. I have difficulty to find information about covariates adjusted for in the Reginster publication from 2005 (ref 16). Can the authors on p 11 (top) indicate variables included in the adjusted analyses?</li> </ol>
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<b>REVIEWER</b>	<p>Jean-Yves Reginster  Department of Public Health and Bone and Cartilage Metabolism  Unit, University of Liège Sart Tilman, 4000 Liège Belgium</p>
<b>REVIEW RETURNED</b>	17-Jun-2014

<b>GENERAL COMMENTS</b>	<p>This paper attempts to find evidence for differences between trial data included in publications on strontium ranelate and data submitted to regulatory agencies. Although the topic is of general interest, the paper is globally insufficiently documented and has a number of important weaknesses. The methodology is simplistic, and based on the publicly available documents from the European Medicines Agency and on a basic bibliographic search. However, the paper does not reflect all available publications, and its conclusions are based on a limited and partial selection of data from literature. Moreover, most of the conclusions are based on regulatory data, even though the authors themselves state that they could not access the entire file for strontium ranelate. This implies that probably a non-negligible quantity of data have not been taken into account in this manuscript. The conclusions and hypotheses of the manuscript should therefore be discarded. Finally, there is a major confusion over reporting of venous thromboembolism and pulmonary embolism (see comment 2), which leads to doubts on the reliability and robustness of the analyses reported by Bolland et al, and on the relevance of their conclusions.</p> <p>In addition, it should be noted that Dr Bolland quotes the name of a single author on page 9 (JY Reginster). JY Reginster has already been cited in a letter to editor from Dr Bolland in the <i>Ann Rheum Dis</i> on the adverse event profile of strontium ranelate (Bolland et al, <i>ARD</i>.2013. 72 (8):i22.). This suggests that the paper may not be entirely objective.</p>
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This paper might be considered for publication but only following major and exhaustive revision, as described below.

**Major comments**

- 1- The author mentioned in the introduction that the the two EMA committees, the PRAC and the CHMP, had divergent opinions. For greater clarity, the role of each committee should be explained in more detail. Indeed, the PRAC is solely responsible for safety assessment, while the CHMP is responsible for a more global benefit/risk assessment and the subsequent delivery of marketing authorization on the basis of their conclusions (and not those of the PRAC). This is not the first – nor is it likely to be the last – time the two committees have reached differing conclusions. The reasons for the discrepancy between the conclusions of the PRAC and the CHMP with regard to strontium ranelate are publicly available (according to the references in the paper), and these reasons should also be discussed in detail in the manuscript.
- 2- There is a major confusion in the paper, since the author differentiates between venous thromboembolism and pulmonary embolism. In the Summary of Product Characteristics of strontium ranelate, it is clearly stated that venous thromboembolism includes pulmonary embolism; they are not considered as two separate entities. This means that the authors should revise all the conclusions and paragraphs regarding pulmonary embolism. For example, in the abstract, the sentence “data on venous thromboembolism were reported in only 5 of 9 primary publications, data on pulmonary embolism is only in 1 of 9 primary publications” is false, and should actually read "data on venous thromboembolism and pulmonary embolism were reported in only 5 of 9 primary publications". All the sections concerned (abstract, results, discussion and box) should be modified in line with this comment. This important modification will necessarily have an impact on the author's conclusion, which should be revised accordingly.
- 3- It is stated in the manuscript that strontium ranelate does not reduce hip fracture, whereas this has been recognized and endorsed by the European Medicines Agency. The sentence in the discussion “it does not prevent hip fractures“ should therefore be removed and publicly available results on hip (from regulatory and from literature) should be added.
- 4- In the results section, the authors refer to analyses performed in a subgroup at greater cardiovascular risk, stating that the "details of this analysis were not reported" (Results section/Page 8/Line 3 and 5). The analyses of this subgroup of patients are indeed publicly available in the references supplied by the authors (reference 4). The results on myocardial infarction in this subgroup should be detailed and the numbers (odds ratio, p value, etc) should

	<p>be given.</p> <ol style="list-style-type: none"> <li>5- The number of myocardial infarctions in patients not presenting any contraindication should be added to Table 1. These data are publicly available (see comment 4, above).</li> <li>6- The results provided in Table 2, the line entitled "CHMP scientific conclusion/PRAC assessment" are incomplete: the authors include the numbers from the PRAC but not those from the CHMP. The complete analysis should be provided for full understanding.</li> <li>7- On page 8, lines 17-26, the author describe how the TROPOS study results at 5 years led to questions from the European Medicine Agency, and how, after assessment from the agency in a so-called FUM, the signal was not considered to raise further concern. This strongly suggests that the information and data provided by the pharmaceutical company answered the questions of the agency. It also suggests that the signal over cardiovascular adverse events may not be very strong, making it more difficult to detect. It should also be recalled that safety assessment in clinical trials is of utmost difficulty due to small numbers of patients exposed and the relatively short trial duration of observation. In the TROPOS study, the main endpoint was efficacy and not safety, the study was neither designed nor powered to detect myocardial infarction, and those cases that did occur were neither adjudicated nor probably reviewed by any cardiologist within the context of the clinical trial. These two issues need to be clarified to a much greater extent in the manuscript.</li> <li>8- The literature search is incomplete. For regulatory documents, the Summary of Product Characteristics is never mentioned, while it is the reference for practicing physicians. As regards publications, a number of publications focusing only on the safety of strontium ranelate in post-marketing observational studies are missing. This is important insofar as none of these studies managed to detect a signal for an increase in cardiac events with strontium ranelate when it was used to treat postmenopausal osteoporosis in general medical practice. This is in line with the general failure of the clinical trials to detect a signal earlier in the product lifetime. At least the following papers should be quoted: <ol style="list-style-type: none"> <li>a. Breart et al. Osteoporosis and venous thromboembolism: a retrospective cohort study in the UK General Practice Research Database. <i>Osteoporos Int</i> 2010;21:1181-1187.</li> <li>b. Cooper et al. Ischaemic cardiac events and use of strontium ranelate in postmenopausal osteoporosis: a nested case-control study in the CPRD. <i>Osteoporos Int</i>. 2014. 25:737-745.</li> <li>c. Svanström H et al. Use of strontium ranelate and risk of acute coronary syndrome: cohort study. <i>Ann Rheum Dis</i> 2014; Epub ahead of print. doi:</li> </ol> </li> </ol>
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	<p>10.1136/annrheumdis-2014-205283.</p> <p>d. Abrahamsen B et al. Nationwide registry-based analysis of cardiovascular risk factors and adverse outcomes in patients treated with strontium ranelate. <i>Osteoporos Int</i> 2014;25:757-62</p> <p>9- According to comment 8, the results section (page 8, lines 50 to 56), should be completed with at least the four above-mentioned references and conclusions should be moderated.</p> <p>10- While the Open Data campaign should be applauded, it seems highly improbable that physicians and patients would select a treatment based on the volume of the reports submitted to agencies, and so it is unlikely that full disclosure of the regulatory documents would have any true impact on current medical practice. The Summary of Product Characteristics and patient leaflet constitute the major source of information on a pharmaceutical drug, and are likely to remain as such. In this context, the conclusion (page 13/lines 35-39) should be reworded more realistically.</p> <p>11- The authors supply numbers extracted from the PRAC opinion in the discussion (page 13 lines 16-22). These should be set against the numbers considered by the CHMP with an explanation for the differences. Efficacy in the PRAC analyses was assessed on a pool of studies that were not necessarily designed to assess nonvertebral fractures (STRATOS was a dose-ranging study with BMD (not fracture) as an endpoint, and SOTI was designed to assess vertebral fractures, i.e. patients aged around 65 who were not at high risk of nonvertebral fractures). The numbers presented by Bolland et al to support their arguments are not the most relevant and biased the conclusion, and this should be clearly stated in the manuscript.</p> <p>12- The paper would be more relevant, if this analysis was performed for other drugs which have been currently granted for the treatment of osteoporosis in Europe.</p> <p><b>Minor comments</b></p> <p>1- Please add a reference for the sentence: By 2010, annual sales of strontium approached €200 million and the drug was approved in &gt;70 countries.</p> <p>2- Methods section line 34-37 and results section line 21-23: the sentences on the availability of the documents on the agency website should be reworded. The documents are not missing; this is simply not the case. As far as I am aware, none of the EMA documents relative to all drugs on the market or under evaluation by the agency, such as reports and FUM, are ever made publically available.</p>
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## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This is a clearly written and important paper with an impact on policy and decision-making. It raises issues about transparency of clinical trials and the regulatory process. I think the case is stated clearly. Among the concerns raised, the most distressing one is that of discrepant data between the regulatory reports and the scientific publications, while differences in the type of adjustment (or no adjustment) between the papers and reports could (I do not know if this is the case) be due to reporting guidelines and due to comments made by reviewers and editors in the process of journal publication.

Response:

We have added this comment into the text of the Discussion:

“... to explain these differences, although it is possible that differences in statistical analyses arose in response to the journal review process.”

This aside, data should absolutely not be discrepant and I think it would be good to add a summary table to highlight the major discrepancies between studies - this can be found by the readers in table 2 but may be missed (footnotes in a busy table).

Response:

We have added a new Box explicitly stating the differences in data between the analyses, and highlighted the Box at relevant places in the Results.

Also, I don't think the abstract is clear enough in terms of mentioning discrepant data - the focus is on discrepant results, which could be statistics not raw data, so I would clarify this here too.

Response:

We have clarified this sentence in the abstract:

“There were differences in participant numbers, fracture cases, and venous thromboembolism cases between regulatory documents and primary publications.

I am not sure why there is an appendix of review articles that have addressed strontium. I think this can be removed without any loss of impact.

Response:

While we acknowledge the Reviewer's point, we intend the Appendix as an online data supplement that provides the References for Paragraph 4 of the Results. We think it is important that readers are able to verify the statements made in that paragraph. We have therefore retained the Online Appendix but would be happy to delete it if the Editor wishes.

Reviewer: 2

This overview about strontium ranelate is well written and an interesting reading. Documentation of the discrepancy between officially published and unpublished serious adverse events in clinical trials is of substantial importance for both patients and health professionals.

Some minor issues:

1. P 9, line 7. Can the authors provide reference numbers to the statements (sentence beginning with “Of the 6 economic analyses, .....”

Response:

We have clarified that these papers are in the Economic analyses section of the Appendix.

2. Is it possible to provide information on how the adverse events were defined and identified? Was a clinical events committee used in the trials? Can a change in definition of the adverse events by time in part explain the higher number of adverse events in later documentations?

Response:

This is a very valid point for which we do not know the answer. None of the available documents described definitions or the process by which adverse events were adjudicated. We have added this information to the Discussion.

“It is possible that changes in reported adverse event data between publications arose because of changes in definitions of adverse events over time. Few details are available regarding how the adverse events were identified or defined in individual trials, and whether adjudication took place for any of these events. All data on myocardial infarctions were self-reported. Our experience of adjudicating self-reported myocardial infarctions in a clinical trial where there was an unexpected imbalance of events was that neither the source of the event (hospital discharge code or self-report), nor the level of adjudication substantially altered the relationship between treatment allocation and cardiovascular events.<sup>24</sup>”

3. I have difficulty to find information about covariates adjusted for in the Reginster publication from 2005 (ref 16). Can the authors on p 11 (top) indicate variables included in the adjusted analyses?

We have clarified this in the Results:

“For the primary endpoint for TROPOS, an unadjusted analysis that was statistically non-significant was reported in the regulatory document, whereas in the primary publication a statistically significant analysis adjusted for age, femoral neck bone mineral density, body mass index, and country was reported.

Reviewer: 3

General response

We thank Professor Reginster for his comments. Professor Reginster is the first author of the TROPOS and SEKOIA manuscripts, the final author of the STRATOS and SOTI manuscripts, and the author or co-author of many reviews on strontium ranelate. Because of his intimate involvement with the development of strontium, he offers a unique perspective. We do not share some of his views, and have responded to these in detail below. In general, many of the points Professor Reginster raises are related to his views on whether strontium is effective. This issue is only a minor aspect of our paper with the major focus being the comparison between data published in the regulatory documents with data published in primary publications. In particular, Professor Reginster disagrees with our interpretation of the available data about safety and efficacy of strontium, suggesting that greater weight should be given to post-hoc subgroup analyses contained in regulatory documents that have yet to be published in papers and for which insufficient details are available to allow independent scrutiny, and that greater weight should also be given to published observational studies of strontium. We prefer to focus on intention-to-treat analyses of the primary randomised controlled trials of strontium, which are widely acknowledged as providing the highest level of evidence to inform clinical

practice.

This paper attempts to find evidence for differences between trial data included in publications on strontium ranelate and data submitted to regulatory agencies. Although the topic is of general interest, the paper is globally insufficiently documented and has a number of important weaknesses. The methodology is simplistic, and based on the publicly available documents from the European Medicines Agency and on a basic bibliographic search. However, the paper does not reflect all available publications, and its conclusions are based on a limited and partial selection of data from literature.

Response:

We agree that our methods are simple- a comparison between regulatory documents and published articles- but think that more complex approaches to obtaining information should not be necessary, which is why we support the BMJ's Open data campaign. We have identified all published randomised controlled trials of strontium ranelate, and have clearly identified the unpublished trials in the Box. As outlined in our general response, our focus is on randomised controlled trial data. We do not agree that not including retrospective observational studies is a limitation to our analyses comparing data and analyses of randomised controlled trials reported in regulatory documents with data and analyses reported in primary publications.

Moreover, most of the conclusions are based on regulatory data, even though the authors themselves state that they could not access the entire file for strontium ranelate. This implies that probably a non-negligible quantity of data have not been taken into account in this manuscript. The conclusions and hypotheses of the manuscript should therefore be discarded.

Response:

The Reviewer suggests that because we are unable to obtain a significant body of unpublished data about strontium, our conclusions are invalid. This viewpoint would strengthen our conclusions that all the strontium clinical data and regulatory documents should be made available so these missing data can be assessed, a view consistent with the BMJ's Open data campaign. However, the currently available data, albeit incomplete, do allow assessments of the safety and efficacy, in part because summary data from regulatory publications are available as shown in Tables 1 and 2. Furthermore, comparisons of data from individual trials reported in regulatory documents and published articles are possible. Therefore, we do not see any valid reason for the Reviewer's statement that our hypotheses and conclusions should be discarded.

Finally, there is a major confusion over reporting of venous thromboembolism and pulmonary embolism (see comment 2), which leads to doubts on the reliability and robustness of the analyses reported by Bolland et al, and on the relevance of their conclusions.

Response:

We have addressed this comment below under point 2.

In addition, it should be noted that Dr Bolland quotes the name of a single author on page 9 (JY Reginster). JY Reginster has already been cited in a letter to editor from Dr Bolland in the Ann Rheum Dis on the adverse event profile of strontium ranelate (Bolland et al, ARD.2013. 72 (8): PubMed i22.). This suggests that the paper may not be entirely objective.

Response:

The letter cited uses the long established practice of referring to a publication by the surname of the lead author:

“In the report of their trial of strontium ranelate in knee osteoarthritis, Reginster and colleagues state that “Strontium ranelate was well tolerated” and that “The safety profile of strontium ranelate was satisfactory, in line with knowledge of this agent”.<sup>1</sup> However, contemporaneously, the European Medicines Agency recommended that the use of strontium ranelate be restricted because it increased the risk of myocardial infarction in trials in osteoporosis (relative risk 1.6, 95% confidence interval 1.07 to 2.38), and there was an imbalance in adverse cardiac events with strontium in patients with osteoarthritis.<sup>2</sup> The second statement presumably refers to the trial by Reginster and colleagues.

Can the authors clarify their statements regarding the safety of strontium? What was the risk of cardiovascular events with strontium in this trial, and how does this compare to the trials of strontium in osteoporosis the authors cited as demonstrating a satisfactory safety profile for strontium?”

The section in the current manuscript simply highlighted that the majority of published reviews of strontium ranelate were co-authored by investigators in the clinical trials of strontium, including a high proportion by Professor Reginster. We have removed the name from the text to address Professor Reginster’s concern.

This paper might be considered for publication but only following major and exhaustive revision, as described below.

#### Major comments

1- The author mentioned in the introduction that the the two EMA committees, the PRAC and the CHMP, had divergent opinions. For greater clarity, the role of each committee should be explained in more detail. Indeed, the PRAC is solely responsible for safety assessment, while the CHMP is responsible for a more global benefit/risk assessment and the subsequent delivery of marketing authorization on the basis of their conclusions (and not those of the PRAC). This is not the first – nor is it likely to be the last – time the two committees have reached differing conclusions. The reasons for the discrepancy between the conclusions of the PRAC and the CHMP with regard to strontium ranelate are publicly available (according to the references in the paper), and these reasons should also be discussed in detail in the manuscript.

Response:

The major focus of this paper is the different data in the regulatory documents from the primary publications. The differing decisions between the PRAC and the CHMP form a very minor part of our paper- 1 sentence in the Introduction and half a paragraph in the Discussion. While the reasons behind the differing decisions are of interest, we believe they are beyond the scope of the paper and, as the Reviewer points out, are available in Reference 6.

2- There is a major confusion in the paper, since the author differentiates between venous thromboembolism and pulmonary embolism. In the Summary of Product Characteristics of strontium ranelate, it is clearly stated that venous thromboembolism includes pulmonary embolism; they are not considered as two separate entities. This means that the authors should revise all the conclusions and paragraphs regarding pulmonary embolism. For example, in the abstract, the sentence “data on venous thromboembolism were reported in only 5 of 9 primary publications, data on pulmonary embolism is only in 1 of 9 primary publications” is false, and should actually read “data on venous

thromboembolism and pulmonary embolism were reported in only 5 of 9 primary publications". All the sections concerned (abstract, results, discussion and box) should be modified in line with this comment. This important modification will necessarily have an impact on the author's conclusion, which should be revised accordingly.

Response:

We disagree with this point. Two of the primary publications (MALEO, SEKOIA), and the Cochrane Review do report cases of pulmonary embolism separately from the broader category of venous thromboembolism. Of relevance, Professor Reginster was a co-author on two of these papers. We accept that the manufacturer may have grouped pulmonary embolism under the broader category of venous thromboembolism in some analyses (but also think that this potentially could suit marketing objectives, given the greater clinical morbidity associated with pulmonary embolism). However, we interpret the statement made by the Reviewer that "data on venous thromboembolism and pulmonary embolism were reported in only 5 of 9 primary publications" as stating that data on both venous thromboembolism and pulmonary embolism were reported, which would be incorrect. Once it was clear that strontium increases the risk of pulmonary embolism (which was stated in the initial registration document for strontium, published in 2005, and in the Cochrane review from 2006), we expect that all subsequent publications would have reported these data. We therefore think that the statement that only 2 primary publications reported data on pulmonary embolism is correct, and does not need modification. (Note- there was an error in the abstract which stated 1 of 9 primary papers reported data on pulmonary embolism- this has been corrected to 2 of 9).

3- It is stated in the manuscript that strontium ranelate does not reduce hip fracture, whereas this has been recognized and endorsed by the European Medicines Agency. The sentence in the discussion "it does not prevent hip fractures" should therefore be removed and publicly available results on hip (from regulatory and from literature) should be added.

Response:

Table 2 in our manuscript shows that strontium does not reduce the risk of hip fracture in either the regulatory analyses or the pooled analyses of published data. Thus, our statement is correct.

The analysis the Reviewer refers to is a post-hoc subgroup analysis. In the initial regulatory document, it states: "The CPMP asked the applicant to present data also for the subset with established osteoporosis (i.e. BMD T-score <-2.5 and prevalent fragility fracture). In response to the request and based on a posteriori analysis, the applicant proposes a revised target population for hip fracture prevention: women  $\geq 74$  years and with femoral BMD T-score <-3 (<-2.4 NHANES III)."

The recommended approach to subgroup analyses is to perform a test of interaction, and only to consider data in individual subgroups if the interaction test is significant. Even then, post-hoc subgroup analyses are usually only considered exploratory. We have no information about whether this recommended approach was followed, or whether other possible subgroups were considered before the final age and BMD thresholds were chosen. Given the lack of information about these analyses, and the well-known problems with subgroup analyses, we do not think there is any reason to give these analyses higher or equal priority to the standard unadjusted, intention-to-treat analyses.

4- In the results section, the authors refer to analyses performed in a subgroup at greater cardiovascular risk, stating that the "details of this analysis were not reported" (Results section/Page 8/Line 3 and 5). The analyses of this subgroup of patients are indeed publicly available in the references supplied by the authors (reference 4). The results on myocardial infarction in this subgroup should be detailed and the numbers (odds ratio, p value, etc) should be given.

Response:

We have expanded this sentence to clarify our meaning. "This analysis was a post-hoc subgroup analysis, but no details were provided about how variables were chosen for the analysis, whether an interaction test was performed for the final analyses, what effect size the analyses had power to detect, or whether the analyses were subjected to independent statistical review." Despite the Reviewer's comments, there were no detailed results published about the analysis in reference 4:

"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 text implies that the MAH engaged in exploratory, hypothesis-generating analyses to identify a population subgroup for which strontium administration is safe, which is consistent with the description in reference 6 of "a number of exploratory post-hoc subgroup analyses."

5- The number of myocardial infarctions in patients not presenting any contraindication should be added to Table 1. These data are publicly available (see comment 4, above).

Response:

We think this comment is tangential to the focus on the paper. These analyses have not been reported in a published paper, and given that our aim was to compare data from regulatory documents with published papers, the addition of these data seems irrelevant. Furthermore, the analysis the Reviewer refers to is described in Reference 6 as one of "a number of exploratory post-hoc subgroup analyses". The number of myocardial infarctions captured in this analysis is 30 compared to 104 in the entire cohort and no interaction tests were reported between the population with and without contraindications. Therefore, we see little reason to include results from inadequately reported, exploratory, post-hoc, subgroup analyses which are considerably underpowered to answer the questions posed. For these reasons, we have not added these analyses, preferring to retain the focus on the standard unadjusted, intention-to-treat analyses.

6- The results provided in Table 2, the line entitled "CHMP scientific conclusion/PRAC assessment" are incomplete: the authors include the numbers from the PRAC but not those from the CHMP. The complete analysis should be provided for full understanding.

Response:

We have reviewed the CHMP report of reference 6 and cannot find any analyses regarding fracture efficacy that are relevant to this Table. While some data were reported in the CHMP report section of reference 6 about fracture efficacy in the TROPOS study, these data have previously been reported in other regulatory publications.

7- On page 8, lines 17-26, the author describe how the TROPOS study results at 5 years led to questions from the European Medicine Agency, and how, after assessment from the agency in a so-

called FUM, the signal was not considered to raise further concern. This strongly suggests that the information and data provided by the pharmaceutical company answered the questions of the agency. It also suggests that the signal over cardiovascular adverse events may not be very strong, making it more difficult to detect. It should also be recalled that safety assessment in clinical trials is of utmost difficulty due to small numbers of patients exposed and the relatively short trial duration of observation. In the TROPOS study, the main endpoint was efficacy and not safety, the study was neither designed nor powered to detect myocardial infarction, and those cases that did occur were neither adjudicated nor probably reviewed by any cardiologist within the context of the clinical trial. These two issues need to be clarified to a much greater extent in the manuscript.

Response:

We think the Reviewer's comment supports our call for full disclosure of the relevant clinical study reports and regulatory documents. The BMJ Open data campaign has identified a number of examples where important adverse effects of agents have been not reported by pharmaceutical companies, and there are well-known examples where pharmaceutical companies have misled regulatory authorities, as documented on the BMJ website. Thus, if the Reviewer is correct, releasing these documents will reassure clinicians and patients that all parties acted with appropriate care in assessing the cardiovascular safety of strontium in the TROPOS trial. We think our description of the process in Paragraph 2 of the results adequately addresses the issues and Readers will be able to judge for themselves about the adequacy of the pharmaceutical company and regulatory reviews. We are continuing our efforts to obtain the appropriate regulatory documents which may add further information about the cardiovascular safety assessment that took place in 2007.

With regards to the comments about myocardial infarction, we do not think that the imbalance of myocardial infarctions in TROPOS should have been difficult to detect. There were 58 vs 30 self-reported myocardial infarctions by 5 years which was highly statistically significant and of clear clinical importance. We do not think that the lack of adjudication means the results should have been dismissed, now or at the time. It is very likely too late to adjudicate events in TROPOS now, but it almost certainly would have been possible to do so closer to the completion of TROPOS. We have added a comment about the role of adjudication of adverse events to Paragraph 2 of the Discussion.

"All data on myocardial infarctions were self-reported. Our experience of adjudicating self-reported myocardial infarctions in a clinical trial where there was an unexpected imbalance of events was that neither the source of the event (discharge code vs self-report), nor the level of adjudication substantially altered the relationship between treatment allocation and cardiovascular events.<sup>24</sup>"

8- The literature search is incomplete. For regulatory documents, the Summary of Product Characteristics is never mentioned, while it is the reference for practicing physicians. As regards publications, a number of publications focusing only on the safety of strontium ranelate in post-marketing observational studies are missing. This is important insofar as none of these studies managed to detect a signal for an increase in cardiac events with strontium ranelate when it was used to treat post-menopausal osteoporosis in general medical practice. This is in line with the general failure of the clinical trials to detect a signal earlier in the product lifetime. At least the following papers should be quoted:

- a. Breart et al. Osteoporosis and venous thromboembolism: a retrospective cohort study in the UK General Practice Research Database. *Osteoporos Int* 2010;21:1181-1187.
- b. Cooper et al. Ischaemic cardiac events and use of strontium ranelate in postmenopausal osteoporosis: a nested case-control study in the CPRD. *Osteoporos Int*. 2014. 25:737-745 PubMed .
- c. Svanström H et al. Use of strontium ranelate and risk of acute coronary syndrome: cohort study. *Ann Rheum Dis* 2014; Epub ahead of print. doi: 10.1136/annrheumdis-2014-205283.
- d. Abrahamsen B et al. Nationwide registry-based analysis of cardiovascular risk factors and adverse

outcomes in patients treated with strontium ranelate. *Osteoporos Int* 2014;25:757-62

Response:

We do not agree with the Reviewer that our literature search was incomplete. As stated under our general response, we do not think that retrospective observational studies are relevant to the primary focus of the paper which is the comparison between data from the regulatory documents and primary publications of randomised controlled trials. Observational studies can generate hypotheses, but not rigorously test them. Further three of the papers were only published after our paper was submitted. We did review the summary of product characteristics but did not think the limited information relevant to our analyses in this document contributed any new information not already included in other regulatory documents which reported relevant data and analyses in much more detail.

We strongly disagree with the Reviewer's assertion that there was a "general failure of the clinical trials to detect a signal earlier in the product lifetime". There was an increased risk of venous thromboembolism and myocardial infarction with strontium in the Phase 3 clinical trials, which were the only studies adequately powered to detect such effects. Our paper highlights the underreporting of these risks in primary publications about strontium, and subsequent review articles. It is apparent that inadequate reporting of these risks distorted the risk/benefit profile of strontium.

9- According to comment 8, the results section (page 8, lines 50 to 56), should be completed with at least the four above-mentioned references and conclusions should be moderated.

Response:

We have addressed this issue in our general response and under point 8.

10- While the Open Data campaign should be applauded, it seems highly improbable that physicians and patients would select a treatment based on the volume of the reports submitted to agencies, and so it is unlikely that full disclosure of the regulatory documents would have any true impact on current medical practice. The Summary of Product Characteristics and patient leaflet constitute the major source of information on a pharmaceutical drug, and are likely to remain as such. In this context, the conclusion (page 13/lines 35-39) should be reworded more realistically.

Response:

We do not share the Reviewer's pessimistic view of the effect of the Open data campaign. We agree that individual clinicians and patients may not refer to the clinical trial reports, but we believe that independent academic clinicians who write reviews and undertake systematic reviews will do, as will panels providing evidence for guideline developers. Such papers and guidelines are likely to influence the views of clinicians and patients. We therefore think that our conclusion "We suggest that full disclosure of the strontium clinical trial data and regulatory documents be undertaken to allow clinicians and their patients to decide whether use of the drug is worthwhile" is reasonable and realistic. We note the recent analysis of Tamiflu published under the BMJ Open data campaign was based entirely on clinical study reports.

11- The authors supply numbers extracted from the PRAC opinion in the discussion (page 13 lines 16-22). These should be set against the numbers considered by the CHMP with an explanation for the differences. Efficacy in the PRAC analyses was assessed on a pool of studies that were not necessarily designed to assess nonvertebral fractures (STRATOS was a dose-ranging study with BMD (not fracture) as an endpoint, and SOTI was designed to assess vertebral fractures, i.e. patients aged around 65 who were not at high risk of nonvertebral fractures). The numbers presented by

Bolland et al to support their arguments are not the most relevant and biased the conclusion, and this should be clearly stated in the manuscript.

Response:

We have reviewed reference 6 and cannot find numbers in the CHMP analysis that supersede the PRAC analyses. Therefore, we think these numbers are correct, relevant and not biased. The extra-analyses considered by the CHMP included observational studies, and post-hoc exploratory subgroup analyses, which we think are much more likely to be biased than meta-analyses of randomised controlled trials undertaken using the intention to treat principle. We note that the 2006 Cochrane Review, of which Professor Reginster was the senior author, pooled data from the STRATOS, SOTI, and TROPOS trials, in a similar approach to the PRAC analyses. In considering important clinical outcomes, including as much of the available data as possible is recommended.

12- The paper would be more relevant, if this analysis was performed for other drugs which have been currently granted for the treatment of osteoporosis in Europe.

Response:

While we agree with the Reviewer that this would be a worthwhile project, we think it is beyond the scope of this manuscript to do so.

Minor comments

1- Please add a reference for the sentence: By 2010, annual sales of strontium approached €200 million and the drug was approved in >70 countries.

Response:

We have referenced the sentence, as suggested.

2- Methods section line 34-37 and results section line 21-23: the sentences on the availability of the documents on the agency website should be reworded. The documents are not missing; this is simply not the case. As far as I am aware, none of the EMA documents relative to all drugs on the market or under evaluation by the agency, such as reports and FUM, are ever made publically available.

Response:

We do not understand the Reviewers concern. We stated what we found: "None of the clinical trial reports from any trial of strontium were available on the EMA website." and "None of the pertinent documents - the 5 year TROPOS report, the CHMP or FUM evaluations - are available on the EMA website."

Since 2010, the EMA have released documents publicly, as summarised by Doshi, JAMA Intern Med 173:380-2. Similar documents are readily available on the FDA website. We are continuing in our efforts to obtain the relevant Regulatory documents.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Karl Michaëlsson Department of Surgical Sciences Uppsala University Uppsala Sweden
<b>REVIEW RETURNED</b>	10-Jul-2014

<b>GENERAL COMMENTS</b>	No further comments
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<b>REVIEWER</b>	Bo Abrahamsen  Research Centre for Ageing and Osteoporosis, Department of Medicine M, Glostrup Hospital, Glostrup, Denmark  OPEN - Odense Patient data Explorative Network, Institute of Clinical Research University of Southern Denmark, Odense, Denmark  Grants from or conducted trials for Novartis, Nycomed/Takeda and Amgen. Advisory board member Nycomed/Takeda, Merck and Amgen. Speakers fees from Nycomed/Takeda, Amgen, Merck, Eli Lilly.
<b>REVIEW RETURNED</b>	10-Jul-2014

<b>GENERAL COMMENTS</b>	I am satisfied with the replies and with the additions to the document and have no further comments.
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<b>REVIEWER</b>	Jean Yves Reginster University of Liège
<b>REVIEW RETURNED</b>	22-Jul-2014

<b>GENERAL COMMENTS</b>	My only concern is that, since none of my comments were really taken care of, notwithstanding the response made by Doctor Bolland and colleagues, it might be appropriate to mitigate the conclusion, both in the manuscript and in the abstract. In my opinion, the current very strong formulation of the conclusion is not substantiated by the data and, whereas I perfectly understand the position of the authors, I think that it would be fair and balanced to somehow acknowledge the fact that the article only reflects a limited knowledge of the data which, when available in full, support the conclusion of the previous papers and publications, as well as the opinion, reflected in several occasions, by the European Medicine Agency. As it is currently written, the paper is rather misleading, since it gives the impression that data were deliberately hidden they were made fully available by the Marketing Authorization holder to the Agency and the exhaustive data fully support what was made public, both by the Agency and by the authors of the published articles.
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## VERSION 2 – AUTHOR RESPONSE

Reviewer 1

No further comments

Reviewer2

I am satisfied with the replies and with the additions to the document and have no further comments.

Reviewer 3

My only concern is that, since none of my comments were really taken care of, notwithstanding the response made by Doctor Bolland and colleagues, it might be appropriate to mitigate the conclusion, both in the manuscript and in the abstract. In my opinion, the current very strong formulation of the conclusion is not substantiated by the data and, whereas I perfectly understand the position of the authors, I think that it would be fair and balanced to somehow acknowledge the fact that the article only reflects a limited knowledge of the data which, when available in full, support the conclusion of the previous papers and publications, as well as the opinion, reflected in several occasions, by the European Medicine Agency. As it is currently written, the paper is rather misleading, since it gives the impression that data were deliberately hidden they were made fully available by the Marketing Authorization holder to the Agency and the exhaustive data fully support what was made public, both by the Agency and by the authors of the published articles.

Response

We acknowledge that our views on the safety and efficacy of strontium are different from those of Professor Reginster. This may in part reflect that Professor Reginster was intimately involved in the strontium clinical trials programme whereas we have had no association with strontium or its manufacturer, Servier.

Our conclusion in the Abstract is that “Inadequate reporting of adverse events and fracture efficacy has distorted the risk/benefit profile of strontium in favour of its widespread use.” We think this conclusion is reasonable given the data presented in the manuscript, showing underreporting of data on myocardial infarction, venous thromboembolism, and pulmonary embolism, and differences between data on fracture efficacy amongst regulatory analyses and between regulatory analyses and primary publications. As we show in the paper, the risks of these 3 adverse events from strontium use are similar to the benefits on fracture prevention, which is not reported in any published paper on strontium ranelate. We think that had these adverse events been reported in the primary publications, the risk/benefit profile of strontium would have been considered much more closely, and its use subsequently much less widespread (for example, prescribing of strontium is now restricted to a subset of the population with no history of heart and circulatory problems and who cannot take other osteoporosis medicines). Therefore, we think our conclusion is justified and we prefer to retain the current wording.

We are not certain what the Reviewer means about limited data. We have included all publicly available data from the European Medicines Agency, and all relevant published papers on strontium, and acknowledged the limitations of these data. As discussed in the previous review, we do not think there are other outstanding RCT data, and we do not think observational trials or inadequately described post-hoc exploratory sub-group analyses from regulatory documents should be given

higher weighting than the data we have included in our paper, which represent all available trial-level data from RCTs of strontium ranelate. We agree that it is currently difficult for clinicians and patients to accurately assess the utility of strontium treatment, or the adequacy of data reporting by Servier and the regulatory response by the European Medicines Agency. Full disclosure of the clinical trial data either by Servier or by the European Medicines agency is required to allow these assessments to occur. If this occurred, it would allow assessment of the Professor Reginster's contention that "the exhaustive data fully support what was made public, both by the Agency and by the authors of the published articles".